148 Topics in Current Chemistry

Electrochemistry III

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With 7 Figures and 22 Tables

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This series presents critical reviews of the present position and future trends in modern chemical research. It is addressed to all research and industrial chemists who wish to keep abreast of advances in their subject.

As a rule, contributions are specially commissioned. The editors and publishers will, however, always be pleased to receive suggestions and supplementary information. Papers are accepted for "Topics in Current Chemistry" in English.

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Preface to the Series on Electrochemistry

The scope of electrochemistry having broadened tremendously within the last ten years has become a remarkably diverse science. In the field of electroorganic synthesis, for example, selectivity has been improved by use of electrogenerated reagents, energy uptake lowered and space-time yields have been improved by using mediated reactions. In addition, electroorganic chemistry has been efficiently applied to the synthesis of key building blocks for complex molecules and has established its role as a new tool in organic synthesis. However electrochemistry has also found new and interesting applications in quite different fields of chemistry. Photoelectrochemistry, as one example, is not only valuable for transformations of organic molecules but also for the very important goal of energy conversion. More insight has been gained in the processes occurring on illuminated semiconductor electrodes and micro particles. Designing the composition of electrode surfaces can lead to the selective activation of electrodes. Electrochemical sensors and techniques present new opportunities for the analysis of biological compounds in medicine and biology. Research in the field of conducting polymers is very intensive because of interesting potential applications.

Therefore I am very happy that Springer-Verlag has decided to account for these important developments by introducing a series of volumes on new trends in electrochemistry within its series Topics in Current Chemistry. The volumes will cover the important trends in electrochemistry as outlined above in the following manner:

Electroorganic Synthesis by Indirect Electrochemical Methods;
New Applications of Electrochemical Techniques;
Recent Development in Electroorganic Synthesis.

The guest editor is very happy and thankful that well-known experts who are actively engaged in research in these fields have agreed to contribute to the volumes. It is hoped that this collection of reviews is not only valuable to investigators in the respective fields but also to many chemists who are not so familiar with electrochemistry.

Bonn, Mai 1987 Eberhard Steckhan

Preface to Volume III

At this rather advanced stage of research and application, I think, it is very appropriate to devote Volume III and part of Volume IV of the electrochemistry series in Topics in Current Chemistry to **recent developments in electroorganic synthesis**. The basis for modern electroorganic synthesis was laid down during the 1960's and 70's by the discovery of the principal reaction mechanisms and by the introduction of a number of industrial processes. Now, electrochemists are in a position in which they can select from an abundance of methodological tools to synthesize complex organic building blocks and target molecules.

This is nicely demonstrated by two contributions to this volume. On one hand, electrochemical strategies for the synthesis of complex bioactive alkaloid structures are developed, and on the other, the electrochemical transformation of readily available bio-molecules (terpenoids and β-lactams) into enantiomerically pure complex synthetic building blocks is demonstrated.

In one paper, a new methodology for the remarkably selective reduction of organic molecules, possessing very negative reduction potentials, is developed. Due to the relatively simple reaction conditions, this method may be an interesting alternative to alkali metal-ammonia reductions.

A tremendous amount of research in the field of electroorganic synthesis has been performed in industrial laboratories. This work usually is only accessible with difficulty because it is hidden in patents. Therefore it is extremely helpful for scientists working in this field that an industrial electrochemist undertook the burden of critically reviewing the patent literature. At the same time the prospects and limitations for future industrial applications of electroorganic syntheses are clearly evolved.

It is hoped that the contributions to this volume will fruitfully influence the further development of electroorganic chemistry and initiate a growing interest in the application of electrosynthetic methods.

Bonn, April 1988 Eberhard Steckhan

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Electrochemistry II

Organic Electrosyntheses in Industry

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Dedicated to Prof. Dr. Dörfel on the occasion of his 60th birthday

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The article gives a survey on research in the field of organic electrochemistry in industry Reference is made to the patent literatur of the last 10 to 15 years. Prospects and problems of electroorganic processes are discussed in detail — also in comparison with proven technologies. Furthermore, some general criteria are presented which can be regarded as preconditions for the realization of electroorganic syntheses in industry. Although there has been considerable progress over the past few years and further electroorganic reactions have been implemented in industry, there is still a need for more highly selective electrosyntheses if this technology is to find broader application in industry.

1 Introduction

Up to the present, electrochemical reactions have not formed an important part of industrial organic chemistry although these syntheses are among the oldest reactions of organic chemistry, the Kolbe reaction being an example [1,2]. This situation is in contrast to that encountered in inorganic chemistry. The electroorganic syntheses of lead-tetraethyl [3] and adipodinitrile [4-5] which were realized industrially in the sixties are to some degree exceptions, although only the adipodinitrile process will continue to be important in the future. At that time, the method was expected by many to become widely established in industry; however, this expectation proved false and industrial activities in this new area were once again restricted. The failure was principally due to the virtually exclusive concentration on finding processes for large-scale products.

The unsuccessful efforts to establish an alternative electrochemical process for the synthesis of propylene oxide [6,7] in industry are an example of this. The consistent application of organic reaction mechanisms to electroorganic syntheses (e.g., [8-9]), and the new indirect electrosyntheses [10] with a preparative basis, have been major factors underlying the industrial chemist's increasing awareness of the neglected preparative potential of organic electrochemistry. Thus, activities in this peripheral area of organic chemistry have once again increased over the past few years, although work at present tends to be concentrated in the area of fine chemicals [11].

The past few years have seen the appearance of a number of excellent monographs [12-17] which give a good overview of the preparative potential of organic electrochemistry. While the scientific literature is generally comprehensively covered, the patent literature receives little or no attention. It is hoped that this article will help to close this gap and furthermore review the projects undertaken in industry over the past few years.

2 Prospects and Risks of Electroorganic Reactions in Industry

The prospects of electrochemical reactions in industry depend primarily on their preparative potential and are much less affected by a lack of know-how in the area of electrochemical process engineering or even by management's lack of interest or unwillingness to take risks, as was frequently claimed in the past [18]. In competing with other technologies, organic electrochemistry has made some progress over the past few years. However, even today there are too few reactions which can be carried out either with high selectivities or particularly advantageously only by an electrochemical route. Examples of industrially important reactions are the anodic substitution reactions, which permit the functionalization of olefins and aromatics; the cathodic hydrodimerization of activated olefins and carbonyl compounds, which provides a simple method for C—C coupling; and finally the electrochemical regeneration of expensive, highly selective redox systems, whose stoichiometric application is ruled out for economic or environmental reasons.

From the point of view of process engineering, electrochemical reactions offer a number of advantages: conversion, reaction rate, and, within certain limits, selectivities can be influenced and easily controlled by means of additional parameters, such as current density and charge. Electrochemical reactions take place under mild

reaction conditions (no high temperatures, in general atmospheric pressure) and do not require pressure-tight or corrosion-resistant equipment. This permits comparatively low capital expenditure, at least for the mere synthesis itself. Electrochemical reactions do not in general entail any waste air or wastewater problems. This aspect will become even more important for future investments.

However, these advantages are offset by a number of problems, which may be divided into three groups:

I Electroorganic syntheses require special reactors; the cells used in inorganic electrochemistry are not suitable for electroorganic syntheses in general.
II Electrochemical syntheses are phase boundary reactions. The boundary problems, which are also familiar from heterogeneous catalysis, must be expected especially during continuous operation.
III The necessity of using electrolytes frequently results in expensive separation operations during work up of the electrolysis mixtures. These operations render many electroorganic syntheses uneconomical.

In the past developing an industrial-scale electrosynthesis was directly connected to the construction of an industrial electrolysis cell. Today cells which can be used industrially are commercially available. Examples are the SU cell [19] and cells from Steetley Engineering [20] and Reilly Chemical [21]. Furthermore, the FM 21 cell [22–24], developed for the chloralkali electrolysis, is now offered by ICI for electroorganic syntheses, too. These cells are based on the construction principle of a plate-and-frame cell and can be used as either divided or undivided cells. They are offered as multipurpose cells and are suitable for small and medium size capacities. For large capacities, it is frequently more economical to use a tailor-made cell. For example, Monsanto and BASF use a specially developed cell [5, 25] in the adipodinitrile synthesis. For industrial anodic substitution reactions, in which electrolytes with comparatively low conductivities are used, BASF developed an undivided plate-stack cell [26–29]. The literature describes a number of other cells [30–32] which have not become industrially important, so far. A good review of cells and cell design is given by Danly in [33].

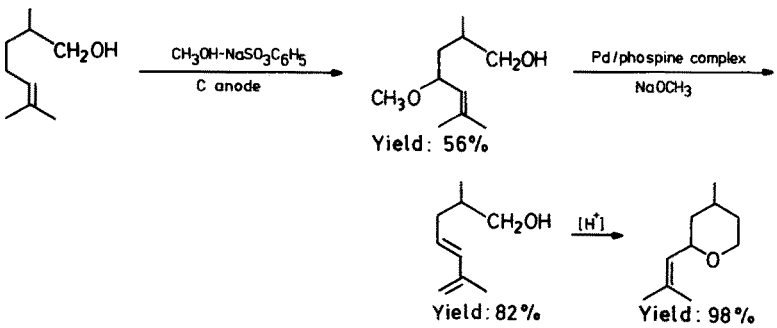
The frequent electrode problems (electrode coatings and deactivation as well as corrosion of electrodes) that occur in continuous operation and the necessity of using auxiliary electrolytes are in many cases the critical problems in the industrial realization of an organic electrosynthesis. Another disadvantage is the very limited possibility of extrapolating experience, gained with one process to the scaling up of new reactions. Therefore, it is generally not possible to dispense with the tedious and hence expensive electrode life tests with simultaneous recycling of the electrolyte. Equally, miniplant technology is only of limited use since long-term tests should as far as possible be carried out on at least one electrode of the planned industrial dimensions. All this has to be considered in advance in order to avoid unpleasant surprises when an industrial plant is commissioned. The problems encountered in scaling up electroorganic reactions are discussed in detail in [34].

3 Recent Work in the Area of Organic Electrochemistry in Industry

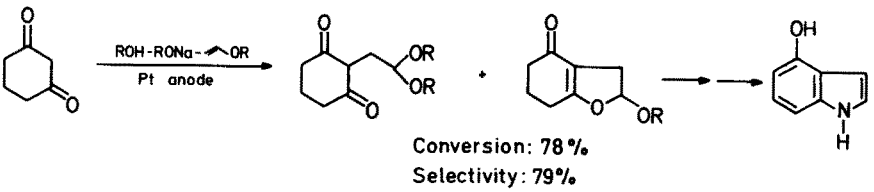
3.1 Anodic Oxidation

3.1.1 Anodic Functionalization of Olefins

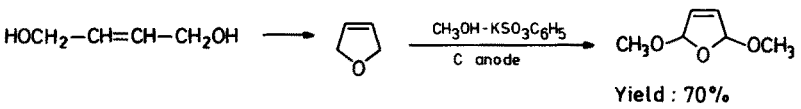
The anodic oxidation of olefins in the presence of nucleophiles, such as CH_3OH or CH_3COOH, is in principle a reaction of very great industrial interest since it permits allyl oxidation as well as C—C coupling. Nevertheless, it is hardly used industrially today. This is essentially due to the fact that the selectivities are frequently poor. Over the past few years, the reaction principle has been used in synthesis problems in the area of fine chemicals. For example, the anodic methoxylation of citronellol is a key step in a new rose oxide synthesis by Sumitomo [35].



Kuraray [36] used the addition of anodically generated radicals of 1,3-dicarbonyl compounds for C—C coupling in the preparation of intermediates for β-blockers.

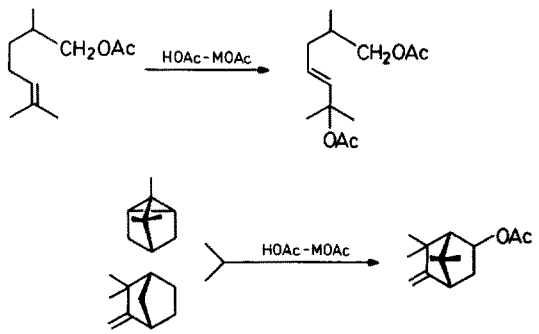


BASF developed a process for the preparation of 2,5-dimethoxy-2,5-dihydrofuran from butene-1,4-diol [37]:

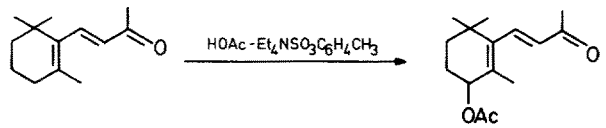


which is an alternative to the anodic methoxylation of furan (cf. 3.1.5).

The anodic acetoxylation of olefinic terpenes was used for the synthesis of new fragrances (Kuraray [38–42])

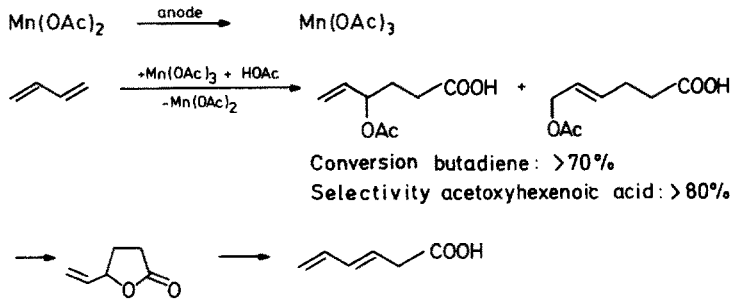


and for the intermediates of canthaxanthin (Hoffmann-La Roche [43]).



Yield: 65%

These reactions — with the exception of [37] — have not progressed beyond the laboratory stage, while a new sorbic acid synthesis based on the addition of carboxymethyl radicals to 1,3-butadiene [44–48] has reached the pilot stage at Monsanto. The core of the new synthesis is the in-cell regeneration of the chemical oxidant $Mn(OAc)_3$ in the presence of catalytic amounts of Cu(II) salts.

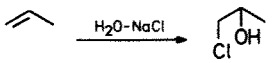


The new synthesis is superior to the present process based on ketene and crotonaldehyde in terms of the variable costs (butadiene and acetic acid are inexpensive starting materials). However, high conductive salt concentrations coupled with low concentrations (2–4%) of the desired product in the electrolyte together with considerable corrosion problems make the working up procedure much more expensive. Therefore, the new process so far has not been used industrially.

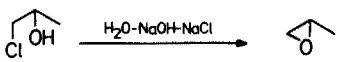
3.1.2 Electrochemical Epoxidation of Olefins

The electrosynthesis of propylene oxide (PO) has already been studied intensively by Bayer [49] in the sixties, and has been scaled up to the pilot scale. The synthesis was carried out in a divided cell at Ti/RuO_2 anodes and steel cathodes.

Anode reaction:

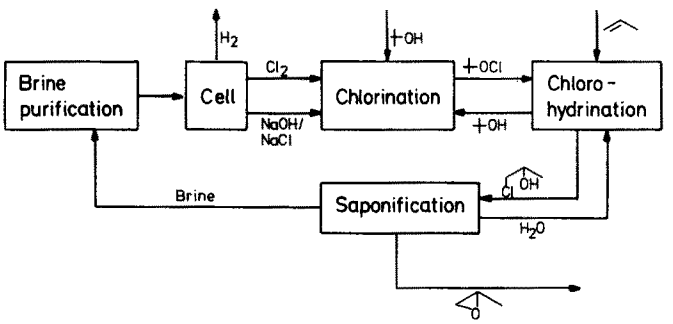


Cathode reaction:



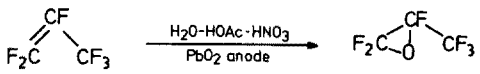
The current efficiencies for propylene oxide were 85 to 90%, and, as in the conventional chlorohydrin process for PO, the principle byproduct was 1,2-dichloropropane (current efficiency up to 10%), which is of no value. Experiments at BASF [50] have shown that the process can also be carried out in undivided cells (anode: Ti/RuO_2 or graphite). The electrolyte was an aqueous NaBr solution. Also in this case, however, it proved impossible to suppress the formation of the 1,2-dibromopropane byproduct. Because of the low concentrations of desired product (2–4% of PO in the electrolyte) and the presence of numerous byproducts, the work-up procedure is complicated rendering the process uneconomical. The addition of carbonates or bicarbonates (UCC [51]) reduces the formation of dibromopropane from about 10 to about 5 mol %, but also in this case the principal problems are not solved. The conventional industrial chlorohydrin process is not very satisfactory as it inevitably produces a large amount of $CaCl_2$. This is why electrochemical alternatives are still searched for. For example, BP has recently proposed a gas diffusion electrode for propylene oxidation [52], and DOW has suggested a special propylene metering system [53].

A more obvious method of avoiding the inevitable production of $CaCl_2$ is the combination of the chloralkali electrolysis with the chlorohydrin process. This is also being pursued intensively [54–55]. A modification proposed by Lummus is shown in the block diagram below [56]:



The electrosynthesis of hypochlorites has been studied in detail by Olin [57–58].

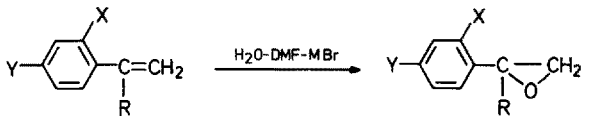
Whereas the electrochemical process of the production of propylene oxide has not advanced beyond the stage of experimental production, the electrosynthesis of hexafluoropropylene oxide [59–62] has been implemented industrially by Hoechst:



Conversion: 65-75%
Selectivity: 90%
Current efficiency: 65%

For the continuous process, a special divided cell (PbO_2/steel anode, steel cathode, Nafion as cation exchange membrane) based on the principle of a tubular reactor was developed. The final product can be removed in gaseous form, so that the electrolyte can be recycled in a simple manner. The membrane and electrodes are supposed to have lifetimes of at least one year [63]. Hexafluoropropylene is a useful monomer for fluorine-containing polymers, e.g., fluorinated polyethers.

The principle of the electrochemical epoxidation can also be applied to complicated structures. For example, ICI [64-65] utilized this reaction for the preparation of intermediates for the synthesis of fungicides.



X,Y: F,Cl
R: alkyl, H

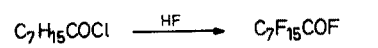
Conversion: >90%
Selectivity: >90%
Current efficiency: about 40%

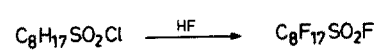
Other recent examples of the versatility of the reaction are syntheses of C6-C17-α-olefin oxides [66], epoxides of terpenes [67], and isosafrol epoxide [68].

3.1.3 Electrochemical Halogenation

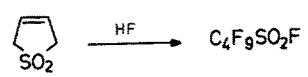
3.1.3.1 Electrochemical Fluorination

In addition to the electrolytic preparation of fluorine, the electrochemical fluorination of carboxylic acid and sulfonic acid derivatives have also become important industrially. The Simons process (Ni anodes, HF as solvent) has been realized industrially by 3 M [69]. The most important products are perfluorooctanecarboxylic and perfluorooctanesulfonic acids, which are used as surfactants and for surface treatments.





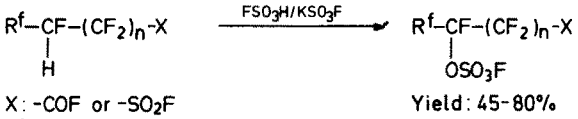
The Italian company Rimar [70] as well as Bayer [71-74] have made particular efforts in this area.



Philips has taken a different direction in the field of electrochemical fluorination. The Philips ECF process uses porous carbon electrodes and KF · 2 HF as an electrolyte. Here, fluorination is effected in the pores of the anodes by electrochemically produced elemental fluorine. The process is therefore suitable for low-boiling products which are substantially insoluble in the electrolyte. The process, which has been successfully tested on the pilot scale, is reviewed by W. V. Childs in [75].

To date, electrochemical fluorination has permitted only perfluorination on an industrial scale, and the selectivities (in some cases less than 50%) are frequently still unsatisfactory. In general, it has turned out that the perfluorinated derivatives are formed in better yields starting from already partially fluorinated compounds than starting from nonfluorinated ones. Up to the present, no electrochemical processes for controlled monofluorination do exist, although the scientific literature [76–77] contains some interesting suggestions (use of $R_3N \cdot xHF$ as electrolytes).

An interesting process for the electrochemical preparation of perfluorinated sulfates has been developed by Hoechst [78–82] on the laboratory scale:



X: -COF or $-SO_2F$
R^f: F or $CF_3-(CF_2)_m-$
n: ≥ 1
m: 0, ≥ 1

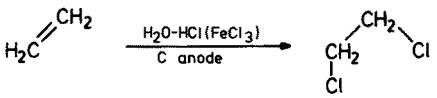
Yield: 45–80%

One of the uses of these products is the preparation of perfluorinated carbonyl compounds.

3.1.3.2 Anodic Chlorination of Olefins

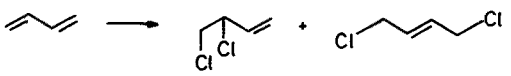
Vinyl chloride and chloroprene (2-chlorobuta-1,3-diene) are among the major intermediates which are produced industrially on the 100,000 tonnes/year scale by thermal chlorination or oxychlorination of ethylene or butadiene.

The electrochemical halogenation of ethylene or butadiene permits substantially milder reaction conditions. Russian studies [83–85] have shown that ethylene can be converted to 1,2-dichloroethane (intermediate of vinyl chloride) in high yields at graphite anodes using aqueous HCl in the presence of small amounts of $FeCl_3$ as electrolyte.



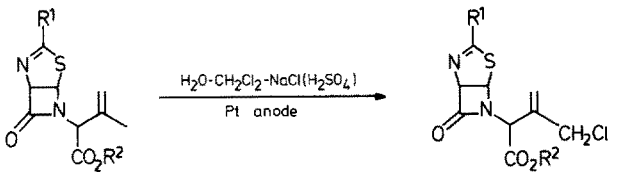
Yield: >97%
Current efficiency: > 95 %

Toya Soda [86–88] has studied the anodic chlorination of butadiene in aprotic electrolytes (e.g. CH_3CN and Fe, Ce, and Ca chlorides).



This yields a 1:1 mixture of 3,4-dichlorobut-1-ene and 1,4-dichlorobut-2-ene with a current efficiency of just under 80%. In the presence of H_2O, dichlorobutanediols are formed [89]. Since electrochemical halogenation did not appear to have any substantial advantages over the established thermal processes, no efforts have been made so far to scale up these reactions.

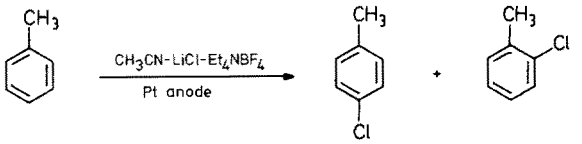
Here again are fairly good prospects for the industrial use of this method in the area of the area of fine chemicals. For example, Torii et al. (Otsuka Patents [90–92]) have used electrochemical allyl halogenation for the synthesis of intermediates for β-lactam antibiotics.



Yield: 93%

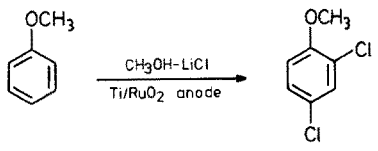
3.1.3.3 Anodic Halogenation of Aromatics

The electrochemical nuclear chlorination of substituted aromatics in some cases allows to achieve better regioselectivities than the chemical alternatives. DOW [93–94] has shown that, in the anodic chlorination of toluene in aprotic electrolytes, the *p/o* ratio of the chlorotoluenes can be increased to about 2.2 (chemical alternatives: 0.5–1, depending on substances added to the reaction mixture):

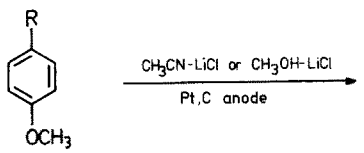


Conversion: about 50%
Selectivity monochlorotoluene: 99%

The use of graphite anodes modified with cyclodextrins allows to increase the *p/o* ratio to above 4 and at the same time to use aqueous electrolytes (NaCl, HCl—H_2O) [95–96]. Electrochemical halogenation has been used in particular by Japanese companies for the synthesis of intermediates on the laboratory scale. A few examples are given below:

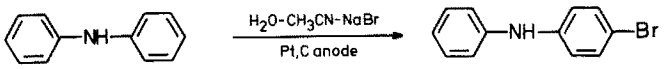


Sugai [97]
Intermediate for agrochemicals

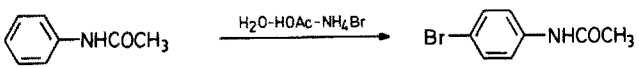


R : alkyl or alkoxy

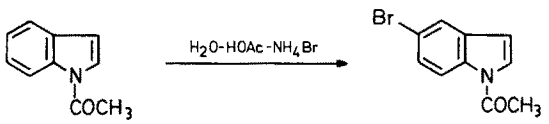
Fuso [98]
Intermediate for pharmaceuticals and agrochemicals



Mitsui [99]
Intermediate for pharmaceuticals and gum

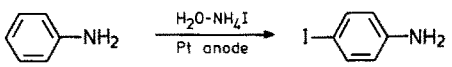


Mitsui [100]
Yield : > 99%



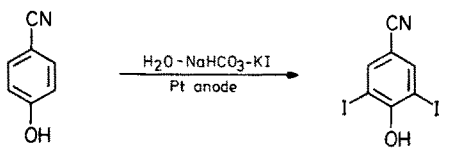
Mitsui [101]

DuPont [102] has used the anodic iodination of aniline as the key step in the formation of *p*-phenylenediamine.



Current efficiency : 91%
p/o ratio : 96 : 4

p-Phenylenediamine is obtained by reaction of 4-iodoaniline with NH_3; thus formed NH_4I can be recycled. The electrochemical step has also been investigated by Asahi [103–104]. Rhone-Poulenc [105] studied the anodic iodination of *p*-hydroxybenzonitrile to form the herbicide Ioxynil:

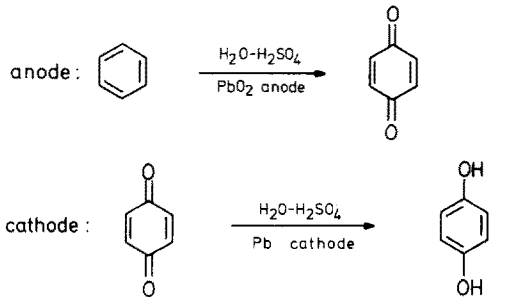


Yield : 97%

3.1.4 Anodic Functionalization of Aromatics

3.1.4.1 Nuclear Substitution

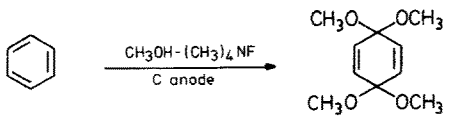
The possibility to functionalize aromatic compounds by electrochemical methods is of great interest to chemical industry. Therefore, considerable efforts were made to develop the electrochemical oxidation of benzene to *p*-benzoquinone to the industrial scale thus forming a basis for a new hydroquinone process. The electrochemical oxidation of benzene in aqueous emulsions containing sulfuric acid using divided cells and PbO_2 anodes forms *p*-benzoquinone. The product can then be reduced cathodically to yield hydroquinone in a paired synthesis.



Conversion of benzene: ≤ 10 %
Selectivity for hydroquinone: 79 %
Current efficiency: 38 %

This reaction was studied intensively by Carus Corp. [106], Electricity Council [107], and in particular by Union Rheinische Braunkohlen Kraftstoff [108]. UK Wesseling has tested a special cell [109] for the reaction on the experimental production scale. However, the process has so far been unable to compete successfully with the H_2O_2 oxidation of phenol or the Hock process. Reasons are the poor benzene conversion, the low quinone concentration in the organic phase (≦5 %), the complicated work up procedure, and the difficult purification of the aqueous phase. Moreover, the electrode lifetimes were unsatisfactory. Nevertheless, the reaction is still of sufficient interest to encourage further attempts to find better solutions. Thus, DOW [110-111] has suggested the use of a special porous electrode made of PbO_2 and polytetrafluoroethylene. This procedure is supposed to give selectivities of 90 % and current efficiencies of 80 % for benzoquinone. A project study for a 10,000 tonnes/year hydroquinone plant has been published by Danly [112].

Hoechst [113-114] took a different approach to the synthesis of *p*-benzoquinone. By oxidation of benzene in methanol solution in the presence of tetraalkylammonium fluorides as conductive salts *p*-benzoquinone tetramethyl ketal is formed. This can be converted to *p*-benzoquinone in a simple procedure while methanol can be recycled.



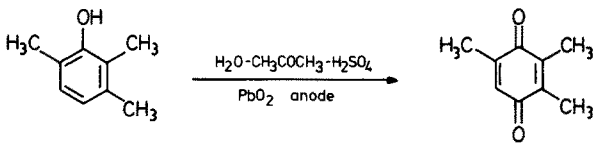
Selectivity: up to 75 %
Current efficiency: 42 %

The best results have been obtained at glassy carbon anodes [115]. The primary intermediate in the synthesis is anisole. Using anisole as starting material instead of benzene the ketal can be obtained in better selectivities (up to 85%) [116].

In addition to the direct electrochemical oxidation of benzene, indirect methods have also been studied. Thus, DuPont [117] has investigated the in-cell regeneration of chromic acid in a divided cell (cathode reaction: reduction of the *p*-benzoquinone solution). However, the current efficiencies for hydroquinone formation (from benzene) are only about 20%. In principle, it is also possible to use phenol as starting material for the synthesis of *p*-benzoquinone or hydroquinone. The higher selectivities (UCC [118–119], conversion based on phenol: 56%, selectivity for hydroquinone: 88%, current efficiency: 40%; Eastman Kodak [120–122], addition of Cr and Cu salts to the electrolyte, special PbO_2 anode) do not, however, compensate for the higher feedstock costs. Furthermore, the work-up procedure is made more complicated by the necessity of separating phenol and hydroquinone.

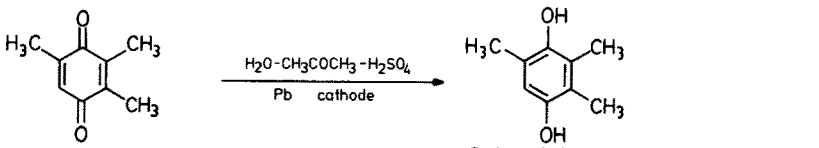
All three types of reactions can also be used for the production of substituted quinones and hydroquinones. For example, BASF has developed two laboratory processes for the synthesis of trimethyl-*p*-benzoquinone and trimethylhydroquinone. The latter is required for the synthesis of vitamin E.

Divided cell [123]
Anode:



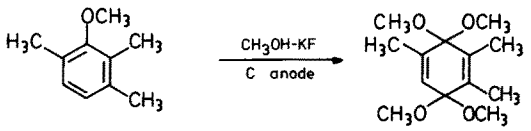
Selectivity : 85%
Current efficiency : 54%

Cathode:



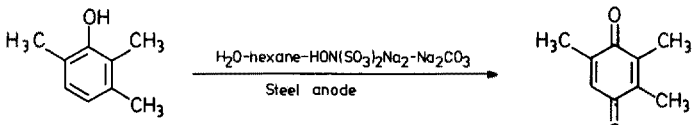
Selectivity with respect to 2,3,6-trimethylphenol: 77%

Undivided cell [124]



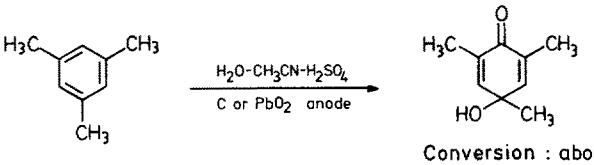
Conversion : 76%
Selectivity: 77%

The best results were obtained in an indirect process [125] developed by Hoffmann-La Roche, in which Fremy's salt was produced electrochemically:

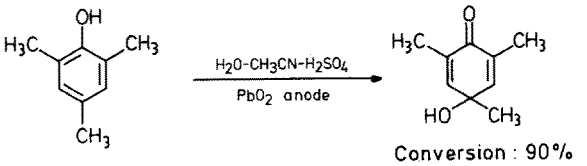


Conversion: > 99%
Yield: 94%

Since regeneration with acceptable turnover numbers has not been possible up to now, this synthesis has not assumed any industrial significance to date. Anic [126–127] and Mitsui [128] describe syntheses of 2,4,6-trimethyl-4-hydroxycyclohexa-2,5-dien-4-one, which can undergo a rearrangement to give trimethylhydroquinone:



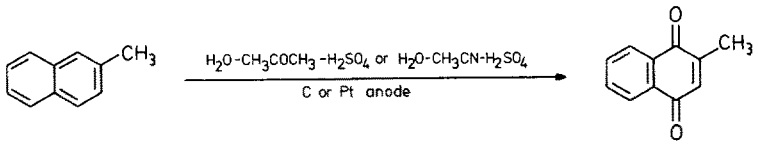
Conversion : about 70%
Selectivity: about 50%



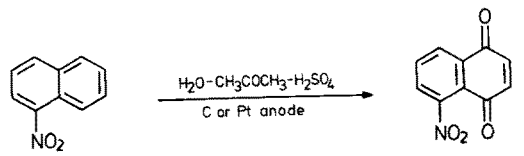
Conversion : 90%
Selectivity: 82%

Intensive efforts have also been made to find an electrochemical process for the synthesis of 1,4-naphthoquinone starting from naphthalene. The aim of this work is to develop a new process for the production of anthraquinone from 1,4-naphthoquinone and butadiene.

The direct oxidation of naphthalenes yields naphthoquinones in poor yields:



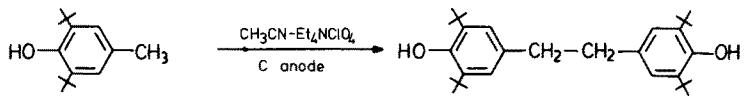
Selectivity : 20-30%
vitamin K [129-130]



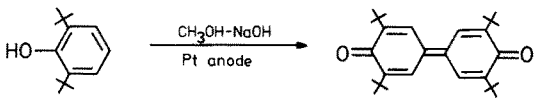
Dye intermediate [131]

Better results were obtained using indirect methods. In addition to chromate regeneration (naphthoquinone: 35–40% selectivity; 2-methylnaphthoquinone: 60% selectivity [132]), in particular Ce(IV) oxidation and regeneration was investigated (ICI [133–134], Ugine Kuhlmann [135], Nippon Shokubai [136], Diamond Shamrock [137]). The best results (naphthoquinone selectivity: >95%, current efficiency for the regeneration: 95%) were obtained using an ex-cell process and cocatalysts (Ag^+, Co^{2+}) in the electrochemical regeneration [138–140]. Because of the poor solubility of the cerium salts, very large reaction volumes are required, however. BC Research Council therefore developed a special undivided cell [141] for the regeneration of a suspension of Ce(IV) sulfate (ratio of anode area to cathode area 10:1). In this case it was necessary to apply and regenerate about 100 l of electrolyte solution per kg of naphtoquinone. Therefore, this process has not been realized industrially up to now.

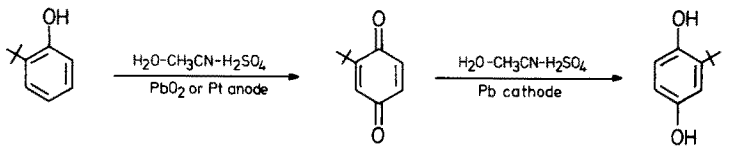
The electrochemical oxidation of substituted phenols was used on the laboratory scale for the production of specialties.



Yield: 79%
Antioxidant [142]

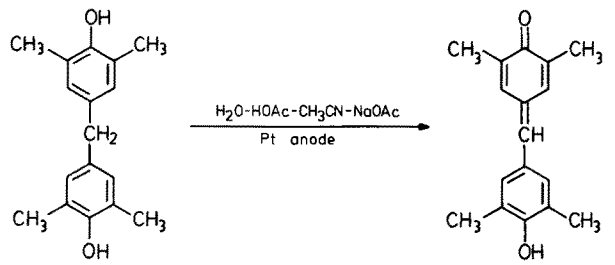


Yield: 94% [143]



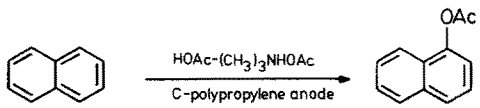
Antioxidant [144]

The synthesis of quinonmethides is claimed by Dow [145]:



Another reaction of industrial interest is the nuclear acyloxylation of aromatics, opening up a new synthetic route to phenols. The reaction was first used by Mobil [146] for the synthesis of naphthyl acetate. The principal problem in this reaction was the

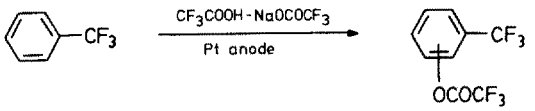
large amount of conductive salts which had to be separated and recycled by expensive methods. Another problem was the formation of methylnaphthalenes and their acetoxylation products by Kolbe electrolysis of the solvent acetic acid. The disadvantages have been substantially overcome by using distillable conductive salts [147] and conductive polymers as electrodes [148].



Undivided cell
Conversion of naphthalene: 20-50%
Selectivity for naphthyl acetate: 70-85%
Current efficiency: 45-65%
ß-naphthyl acetate fraction: 3-5%

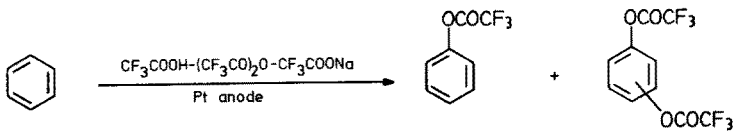
1-Naphthyl acetate can be converted to α-naphthol [149] in a simple manner with recovery of the acetic acid. α-Naphthol is an important intermediate for dyes and insecticides. The new electrosynthesis was successfully carried out on the tonne scale at BASF.

Anodic acetoxylation has also been used for the synthesis of diphenyl esters [150–151] and acyloxyalkoxyaromatics [152–155]. Aromatics with electron acceptors can also be acyloxylated in the presence of trifluoroacetic acid (Hooker [156–158]):



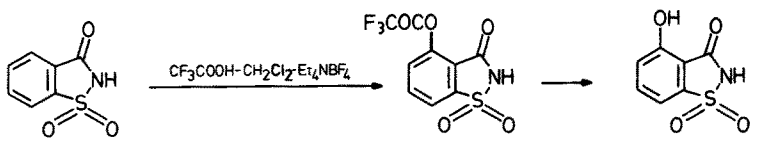
Current efficiency: 57%

If H_2O (about 10%) is added to the electrolyte, the corresponding mixture of phenols is formed with somewhat poorer current efficiencies. Rhone-Poulenc [159] has used this procedure for the acyloxylation of benzene.

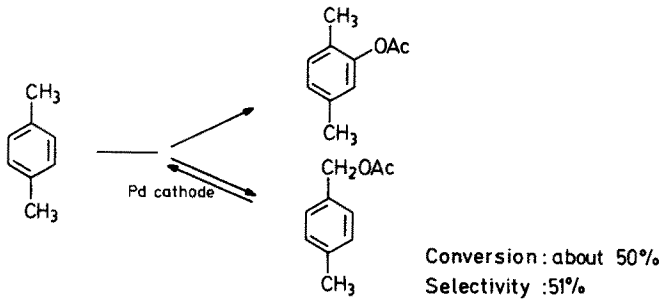


Yield: 12%
o-: 22%
m-: 16%
p-: 31%
Total current efficiency 70%

Thomae [160] has described another trifluoroacetoxylation for the synthesis of a new sweetener on the laboratory scale:

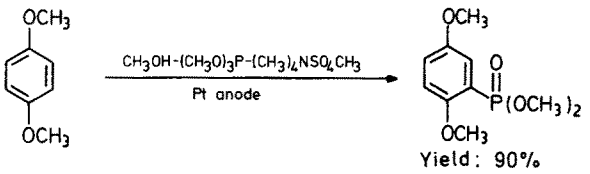


In the case of alkyl-substituted aromatics, the predominant reaction path very often is side-chain acyloxylation. By using Pd-coated cathodes in an undivided cell, it is possible to avoid the formation of the side chain-substituted products, because under these conditions the benzyl ester undergoes cathodic cleavage into the starting compounds [161]:



However, the current efficiencies (about 13%) are unsatisfactory.

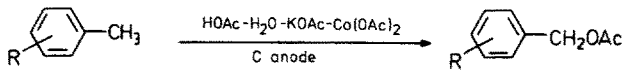
The anodic phosphorylation is another interesting possibility for the functionalization of aromatics. Initially approtic electrolytes (e.g. $CH_3CN/NaClO_4$ [162–163]) were used. Hoechst [164] was also successful in carrying out the synthesis in protic electrolytes.



3.1.4.2 Side-chain Substitution

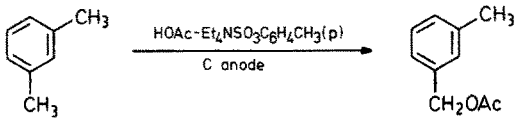
In addition to the cathodic hydrodimerization of activated olefins [see 3.2.1.1], the electrosyntheses of substituted benzaldehydes are among the few electroorganic reactions which are carried out on a large scale industrially.

The anodic acetoxylation of alkyltoluenes was first studied in industry by Mobil Oil [165–167].



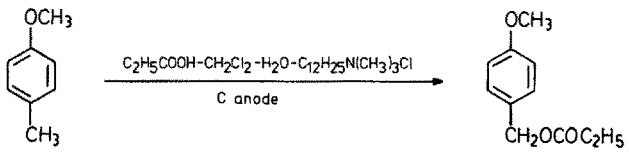
R	Current efficiency
H	61%
3-Cl	52%
4-Cl	66%
3-CN	13%
4-CN	13%
3-CH_3	46%
4-CH_3	62%

Quaternary ammonium salts were used as supporting electrolytes in this reaction by Mitsubishi [168] and others:



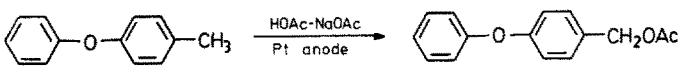
Yield: 64%

UOP [169] carried out the synthesis of anisyl propionate under phase transfer conditions:

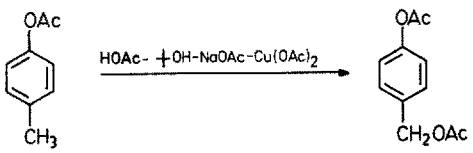


Yield: 34%

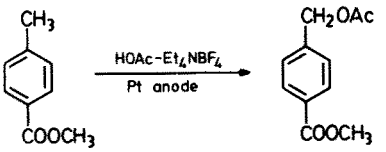
Other examples of this type are summarized below:



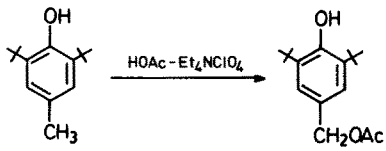
Kuraray [170]
Intermediate for agrochemicals



Otsuka [171]
Intermediate for pharmaceuticals

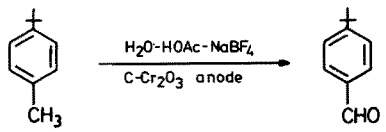


Conversion: 48%
Selectivity : 31%
Intermediate for special polyesters
Standard Oil [172]



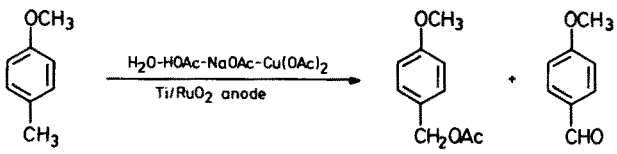
Intermediate for antioxidants
Mitsui [173]

If defined amounts of water are added to the electrolyte, the anodic acetoxylation yields the corresponding aldehydes with very good selectivities. The reaction passes smoothly through the benzyl acetate stage. On the basis of this method, BASF has developed industrial processes for the production of aromatic aldehydes [174–175].



Conversion: quantitative
Yield :87%
Current efficiency :67%

Soda Koryo [176] claims a special electrolyte (*tert.*-butanol-HOAc—Et_4NX—$Cu(OAc)_2$) for the same synthesis, but the yields (77%) are lower. UOP [177] has developed a laboratory process for anisaldehyde based on this method.



Fractions: 82% 18%
Conversion : 18%
Total yield : 50-70%

If the syntheses are carried out in aqueous electrolytes containing sulfuric acid (emulsion method), product mixtures are generally obtained in poor yields [178]. The electro-

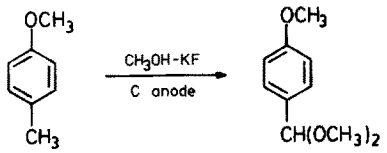
chemical oxidation of 4-*tert*-butyltoluene is an exception and is therefore being studied in more detail by Hoffmann-La Roche and BASF.

Hoffmann-La Roche [179]: Ti/PbO_2 anode
Anolyte: H_2O-CH_2Cl_2-H_2SO_4
Conversion: 83%
Selectivity: 77%

BASF [180]: Pb/PbO_2 anode
Anolyte: H_2O-H_2SO_4
$C_{15}H_{31}SO_3H$ as emulsifier
Conversion: 40%
Selectivity: 70%

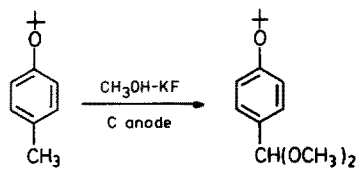
However, the processes require divided cells. This certainly is one of the reasons why they are inferior to the processes using HOAc—H_2O.

If the acetic acid is replaced by methanol in the electrolyte, the electrochemical oxidation yields the corresponding benzaldehyde dimethyl acetals in excellent yields. This reaction which was discovered by BASF [181], can also be used for the industrial synthesis of aromatic aldehydes.

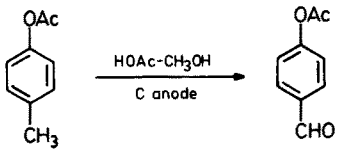


Conversion: quantitative
Yield: >85%

The reaction was also carried out on the laboratory scale by Bayer [182] (use of special electrolytes and collidine as an auxiliary base), Fuso [183] (use of phosphorus compounds as conductive salts) and UOP [184] (use of alcoholates as electrolytes). Under comparable conditions, *p*-cresol cannot be oxidized to the corresponding *p*-hydroxybenzaldehyde derivatives. If the phenolic hydroxyl group is protected, it is also possible to obtain *p*-hydroxybenzaldehyde derivatives.



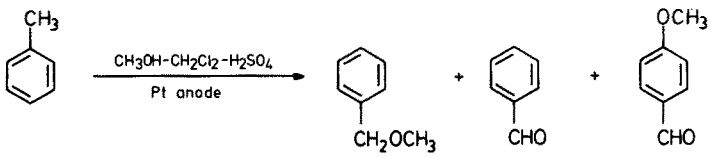
Conversion: 92%
Selectivity: 82%
BASF [185]



Selectivity : 70-80%
(determined by gas chromatography)
Fuso [186]

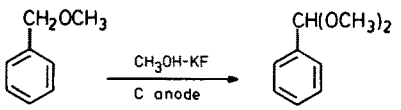
The anodic methoxylation of 4-substituted toluenes to form substituted benzaldehyde dialkyl acetals is widely applicable. Other examples are the syntheses of tolylaldehyde dimethyl acetal (BASF [187]) and 4,4-oxy-bisbenzaldehyde dimethyl acetal (Hoechst [188]).

Toluene itself cannot be oxidized to benzaldehyde dimethyl acetal under similar conditions (Rhone-Poulenc [189]):

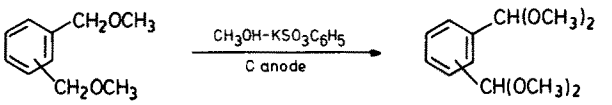


Conversion of toluene : 30%
Selectivities(%): 58 12 20

In contrast, benzyl alkyl ethers (BASF [190]) and bisalkoxymethylbenzenes (BASF [191]) can be converted into the corresponding acetals with very good selectivities:

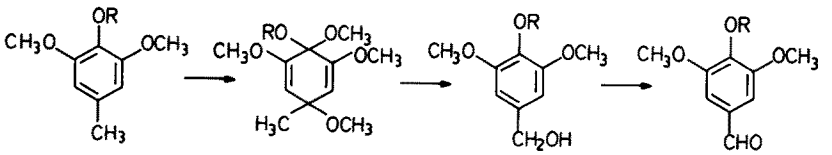


Conversion : 78%
Selectivity :83%



Conversion : 100%
Yield : 80%

Finally, Otsuka carries out two aldehyde syntheses industrially. These syntheses are both based on nuclear oxidation and on side-chain oxidation steps [192].

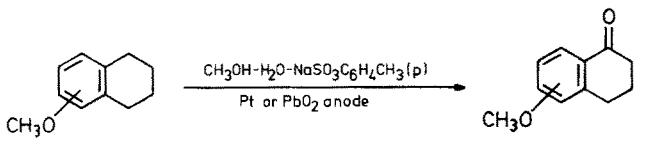


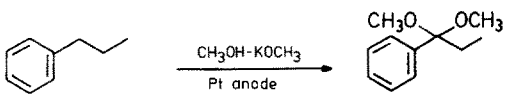
R: -H or -CH3

In addition to the direct electrosyntheses, work also continued on the well known indirect electrosyntheses of aromatic aldehydes by in-cell and ex-cell regeneration of redox systems, such as Mn^{2+}/Mn^{3+} [193-194] and Ce^{3+}/Ce^{4+} [195].

Recent examples for the syntheses of 4-*tert*-butylbenzaldehyde ($Mn^{2+/3+}$—H_2SO_4, Givaudan [196]; Ce^{3+}/Ce^{4+}—HOAc, Otsuka [197]) and anisaldehyde (Mn^{2+}/Mn^{3+}—H_2O—H_2SO_4, UOP [198]; Ce^{3+}/Ce^{4+}—CH_3OH, Otsuka [199], Grace [200]) also show that the principal disadvantages (large reaction volumes, poor space-time yields, considerable problems with working up and recycling the electrolyte, necessity of using divided cells) of this method have not been solved. For example, in the synthesis of anisaldehyde [199], excellent yields of 96.2% are obtained. However it is necessary to separate and recycle 17.6 t of cerium ammonium nitrate and 61 t of methanol per one t of anisaldehyde. Hence, these indirect processes could not be established industrially to date.

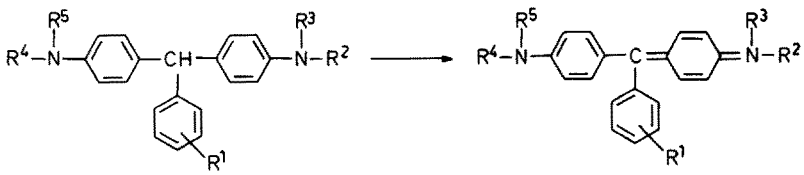
In addition to toluenes, also ethyl benzene derivatives can be converted into the corresponding ketones by similar methods. Work carried out by Schering [201] and UOP [202] are examples.





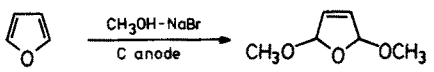
No yield data

Leuco compounds can be converted electrochemically into the corresponding triphenylmethane dyes (e.g. [203-204]).

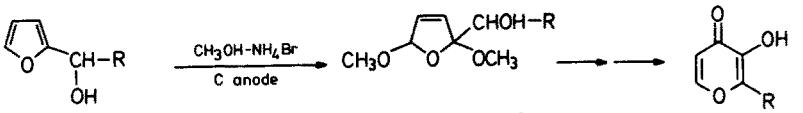


3.1.5 Anodic Oxidation of Heterocyclic Compounds

The electrochemical methoxylation of furans to give the corresponding dimethoxydihydrofurans was discovered by Clauson-Kaas [205] in 1955. This reaction is now carried out industrially by BASF [206] and Otsuka [192].

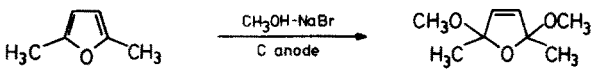


Conversion : 80 %
Selectivity : 96 %



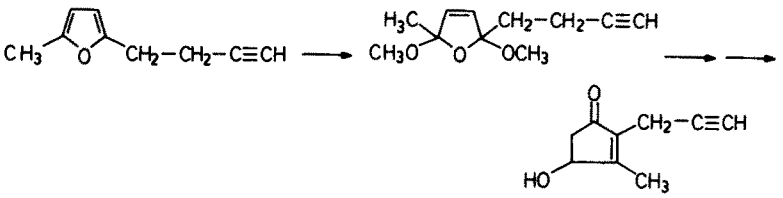
Yield : 73 % [207]
Intermediate for flavors (maltol, ethylmaltol [208-209])

This very elegant reaction was also used on the laboratory scale for the synthesis of biocides (Henkel [210]),

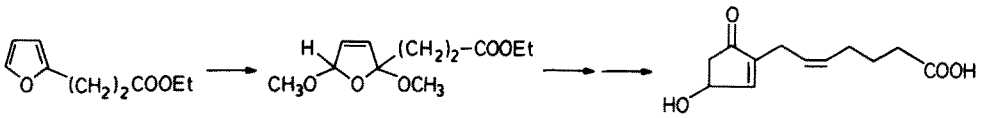


Conversion : 85 %
Selectivity : 89 %

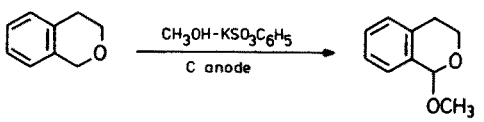
cyclopentenones (Sumitomo [211])



and prostaglandin intermediates (American Cyanamid [212]).

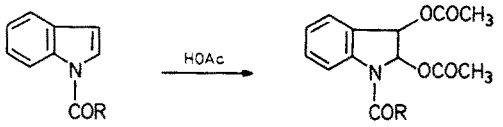


The anodic methoxylation of isochromans was first studied at BASF [213]. This leads to alkoxyisochromans, which can be used for the synthesis of fungicides.

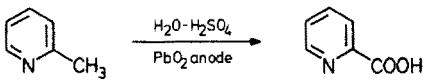


Conversion : 98 %
Selectivity : 75 %

The anodic acetoxylation of N-acylindoles was applied by Mitsui Petrochem. [214-215] to the synthesis of dye intermediates.



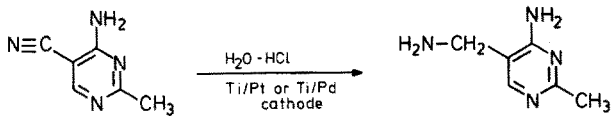
Reilly [216] carries out the electrochemical oxidation of 2-methylpyridine to picolinic acid in divided cells on the industrial scale.



Yield: 80%
Current efficiency: 67%

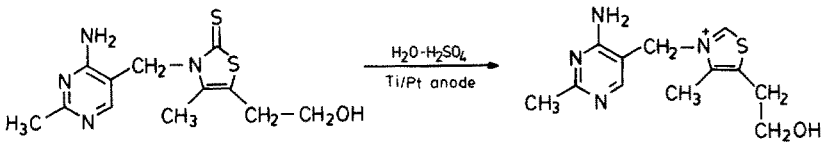
Stamicarbon [217] claims the use of anion exchange membranes in divided cells for the electrochemical oxidation of alkylpyridines to the corresponding pyridinecarboxylic acids. Finally, Takeda [218] has used the principle of paired synthesis in a divided cell for the simultaneous generation of synthetic intermediates.

Cathode reaction:



Conversion : 74%
Selectivity: 97%

Anode reaction:



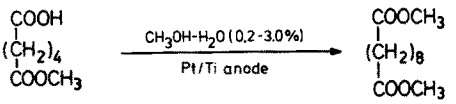
Conversion : 85%
Selectivity: 99%

3.1.6 Anodic Oxidation of Carbonyl Compounds

3.1.6.1 Kolbe Reaction

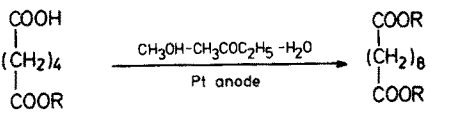
The Brown-Walker version of the Kolbe reaction is the most important reaction of this class. In particular, the anodic oxidation of adipic acid half esters to the corre-

sponding sebacic acid diesters has been studied in more detail (USSR, Asahi [219-222], BASF [223-224]).



Selectivity: up to 93%
Current efficiency: up to 70%
Energy consumption: 2.6 kWh/kg
Current density: 10-30 A/dm²

The process starts from the potassium salt of the adipic acid half ester (about 10 to 30 mol % neutralized). It has successfully been scaled up to the experimental production scale by Asahi. A simplified process scheme for the entire synthesis is shown in [225]. While Asahi was predominantly concerned with the anodic oxidation of monomethyl adipate, BASF mainly worked on the synthesis of sebacates of higher alcohols.

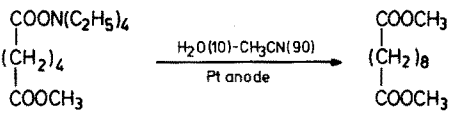


R: 2-ethylhexyl

Yield: 85%
Current efficiency: 65 %
Energy requirement: 3.0 kWh/kg

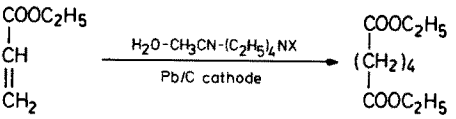
A significant problem in scaling up the Kolbe reaction is the long-term stability of the expensive platinum anodes. Therefore, many attempts have been made to find a a cheaper anode material. One example is the Sowjet work [226], which shows that special carbon anodes can be used. Thus, the loss of carbon in the dimethyl sebacate synthesis (yield: 72.2%) after 8,400 Ah/m² is only 0.008 %. Monsanto [227] has attempted to pair the sebacate synthesis with various cathode reactions.

Anode:



Yield: 87%
Current efficiency: 35%

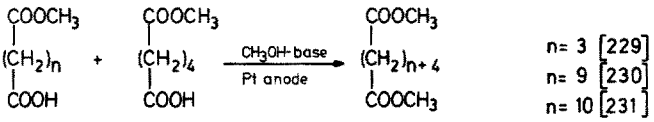
Cathode:



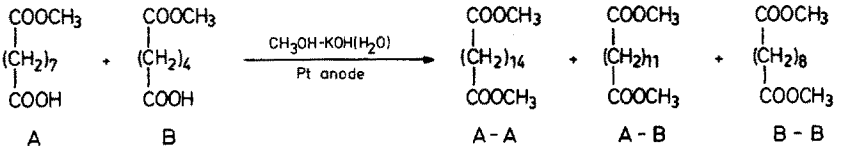
Yield: 84%
Current efficiency: 61%

Presently, the sebacic acid synthesis is carried out industrially only in the USSR (capacity: about 2000 tonnes/year). Fairly large amounts are produced from castor oil, a naturally renewable raw material. The capital costs for large plants are indeed considerable. Sebacic acid is used, for example, as a component in polyamides. Sebacates are used as special plasticizers and synthetic lubricants.

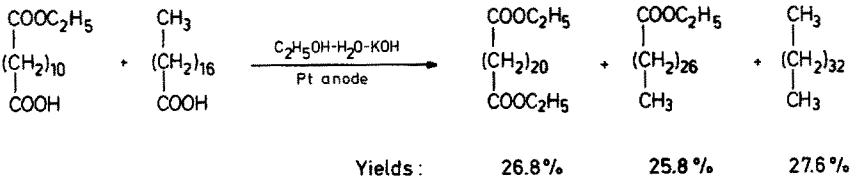
The reaction principle of the Kolbe synthesis can be extended both to higher carboxylic acids (e.g. methyl suberate [228]) and to the dimerization of two different carboxylic acids (cross Kolbe coupling). A few examples of syntheses studied on the laboratory scale are listed below.



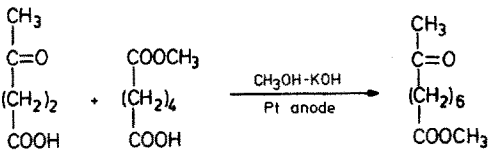
The yield of the cross Kolbe products A — B is generally unsatisfactory [232].



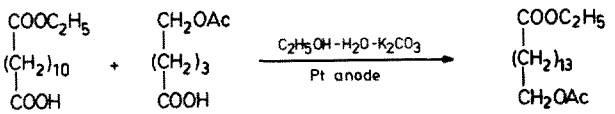
Even with a 4-fold excess of the less valuable component B, components A — A, A — B and B — B are formed in a ratio of 1:8:21. The reaction can also be carried out with monocarboxylic acids [233–235] instead of dicarboxylic acid half esters.



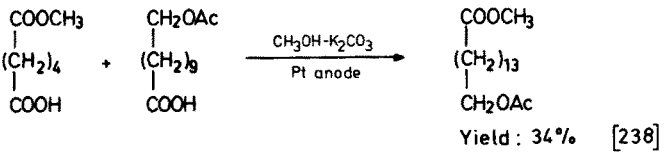
Carboxylic acids with certain functional groups can also undergo the Kolbe reaction.



[236]

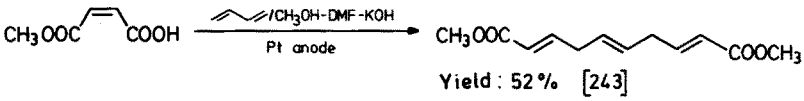


Yield: 16% [237]

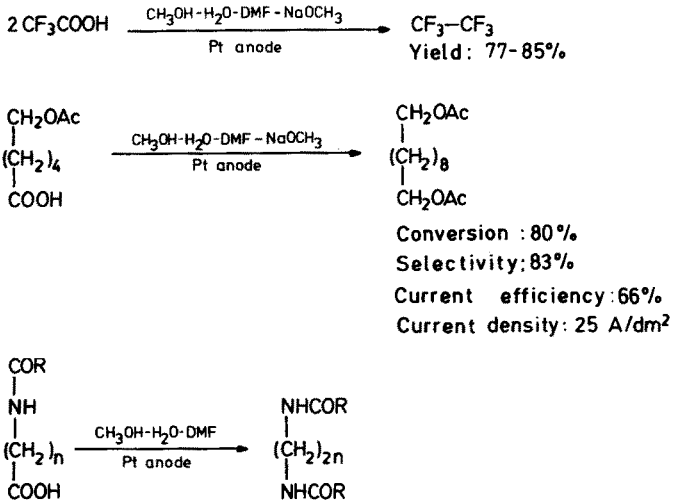


The products of the cross Kolbe reaction are used as plasticizers, intermediates for musk fragrances, etc.

The oxidative addition of carbon radicals formed by Kolbe electrolysis to olefins has likewise been studied on the laboratory scale [239–242].

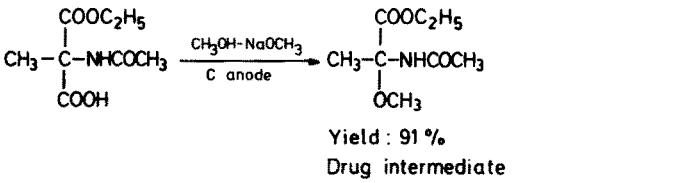


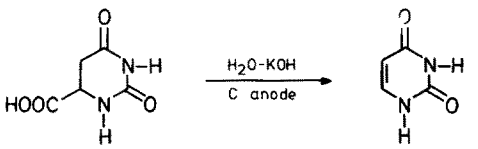
Finally, the Kolbe reaction has also been used for the synthesis of perfluorinated alkanes [244], diols [245], and diamines [246].



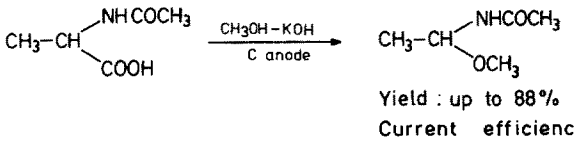
3.1.6.2 Non-Kolbe Reactions

The anodic oxidation of α-substituted carboxylic acids very frequently leads to the two-electron oxidation products instead of the one-electron products. The reaction was investigated in case of a number of amino acid derivatives by Tanabe [247–249] and others.

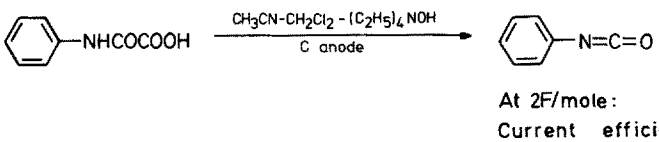




The electrosynthesis of N,O-acetals was investigated by Hoechst [250]. However, this route cannot compete with the anodic methoxylation of carboxamides.

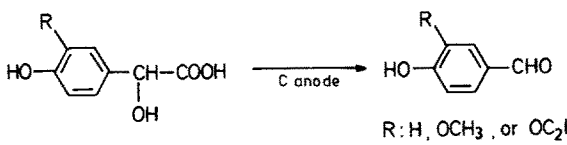


At Shell [251], this reaction principle was applied to a novel isocyanate synthesis:

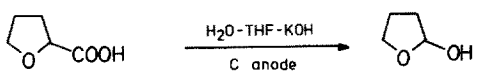


If methanol is used as solvent, the corresponding urethanes are formed (conversion: 73%; yield: 69%; current efficiency: 45%).

Mandelic acids can be converted to the corresponding benzaldehydes [252]:

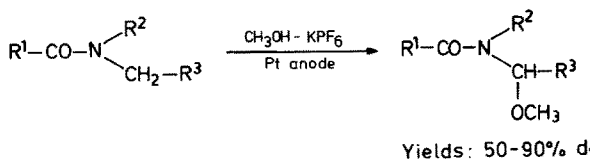


A laboratory synthesis for vanillin is based on this procedure. 2-Hydroxytetrahydrofuran, an intermediate for cytostatics, was produced from the corresponding carboxylic acid by electrochemical oxidation [253]:

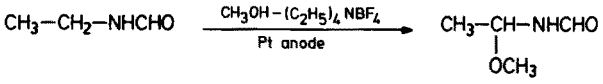


3.1.6.3 Anodic Alkoxylation of Carboxamides

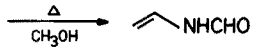
Hoechst [354] has intensively studied the anodic alkoxylation of N-substituted carboxamides.



The investigations primarily concentrated on the electrochemical oxidation of N-ethylcarboxamides [255-256], since the oxidation products open up new synthetic pathways to N-vinylamides [257]:



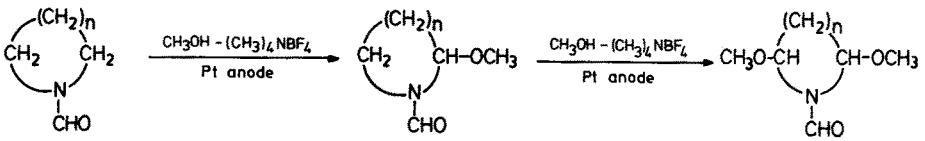
Yield : 70-74%
Current efficiency : 21-27%



If glassy carbon anodes are used, the current efficiencies can be increased to almost 50% [258]. The N-vinylcarboxylic acid derivatives are useful as monomers for basic ion exchangers and for the production of water-soluble cationic polymers.

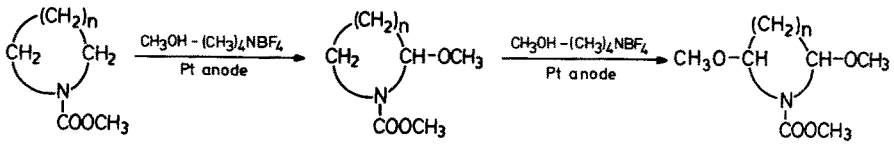
Bayer [259-260] used a similar procedure to produce the corresponding N-vinylurethanes, which are very difficult to obtain by other routes.

The reaction principle was also extended to N-acyl derivatives of cyclic amines by Hoechst [261-262]:



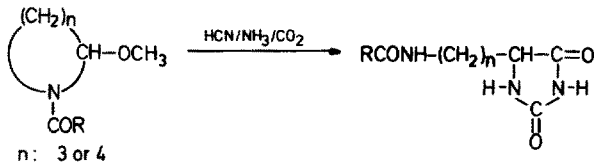
n=3 : Yield:	92.9 %	86.6 %
Current efficiency :	92.9 %	45.6 %
n=2 : Yield:	86.6 %	
Current efficiency:	86.6 %	

The alkoxylated urethanes [263] are formed in a similar manner, in very good yields:

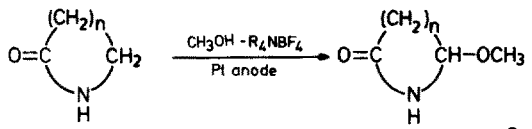


n=3: Yield:	92.5 %	84.3 %
Current efficiency:	73.7 %	60.2 %
n= 2: Yield:	92.6 %	77.5 %
Current efficiency:	74.1 %	47.7 %

The N,O-acetals are intermediates for the synthesis of enamides [264] and for the production of DL-ornithine [265-266] and DL-lysine [267-268]. The amino acid syntheses are not economically competitive with the fermentation methods since they only give the racemates, which then have to be resolved into the antipodes.

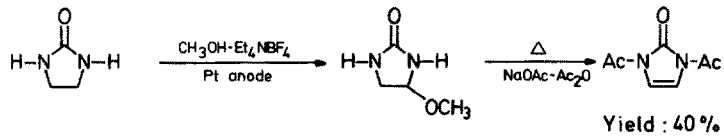


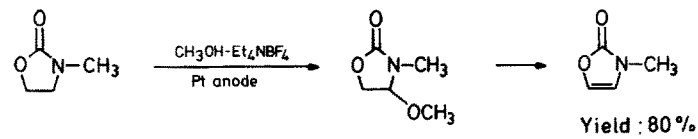
Under comparable conditions lactams were converted to the corresponding N,O-acetals [296–270].



n	Yield	Current efficiency
1	51 %	41 %
2	50 %	50 %
3	72 %	59 %
4	72 %	48 %
6	57 %	38 %
10	51 %	29 %

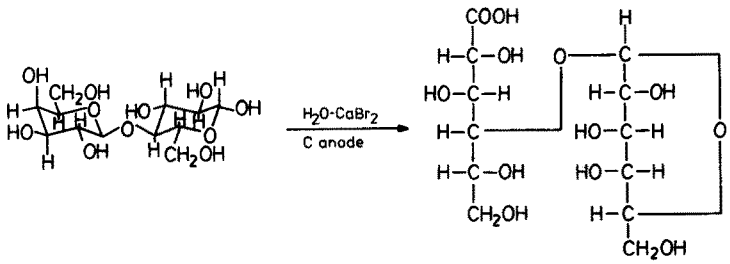
The reaction was applied to the synthesis of compounds with prostaglandin-like properties [269]. It was also employed for the production of ω,ω′-dialkoxycarboxylates and -carboxamides [271]. Dow [272] has extended the reaction principle to a number of 5-ring heterocyclic compounds containing 2 hetero atoms:





3.1.6.4 Anodic Oxidation of Aldehydes to Carboxylic Acids

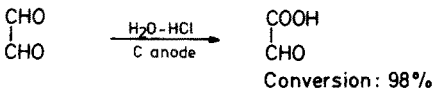
The indirect electrochemical oxidation of aldoses to the corresponding aldonic acids [273–274], which was carried out industrially as early as about 1930, is still used today for production on the tonne scale by Sandoz [275] and in India [276]. Specific examples are the anodic oxidation of lactose to calcium lactobionate [275, 277–278]:



Yield: > 90%

and the production of Ca and Na gluconate by electrochemical oxidation of glucose [276]. Most of the gluconic acid and its salts (market volume: about 30,000 tonnes/year), however, is now produced by fermentation of glucose.

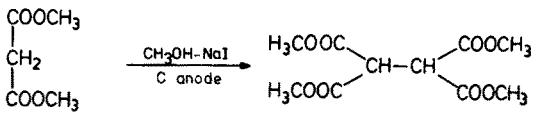
Since aldehydes can generally be converted to the corresponding carboxylic acids in very good yields and in a simple manner by catalytic air oxidation, electrochemical syntheses are not of much interest to the chemical industry. The controlled electrochemical oxidation of glyoxal to glyoxylic acid is an exception [279–280]:



Conversion: 98%
Selectivity: 82%

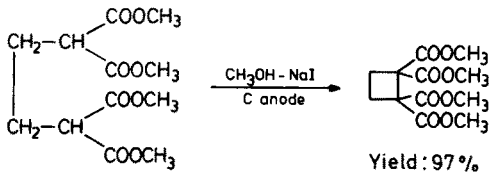
3.1.6.5 Anodic Dimerization of Malonic Acid Derivatives

In addition to the cathodic hydrodimerization of activated olefins and the Kolbe reaction, the anodic dimerization of CH-acidic compounds is another possibility for the electrochemical C—C coupling. Monsanto [281] has used the anodic dimerization of malonates in a laboratory synthesis of intermediates for useful sequestrants and detergency builders.



Conversion: 70%
Selectivity: 98%

The synthetic principle was also used for the production of cyclobutane derivatives:

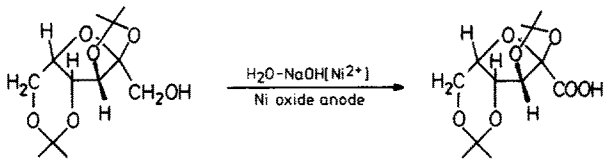


Yield: 97%

3.1.7 Anodic Oxidation of Alcohols and Aliphatic Ethers

3.1.7.1 Electrosynthesis of Carboxylic Acids

Alcohols can be converted electrochemically into the corresponding carboxylic acids in very good yields if Ni oxide anodes are used in alkaline electrolytes. This reaction was studied intensively in industry for the electrochemical oxidation of diacetone-L-sorbose to diacetone-2-ketogulonic acid (intermediates of the vitamin C synthesis). On the basis of Sowjet work [282-284] (initially Pt anodes and NaBr—NaCl—$NiCl_2$—NaOH electrolytes; subsequently Ni oxide anodes), Roche and Merck studied the synthesis on the laboratory and pilot scale. In cooperation with the ETH Zurich [285-286], a special cell [287-288] was developed for this reaction.



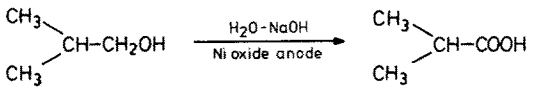
Conversion: >90%
Yield: 93%
Current efficiency: 70%
Energy consumption: 1.2 kWh/kg

Using this procedure, Roche successfully operated a pilot plant for a capacity of tonnes/day for several thousand hours. By adding very small amounts of Ni salts, it was possible to maintain the anode activity over long periods. The electrochemical process is said to be superior to the conventional hypochlorite process, particularly because of the low level of wastewater pollution [286]. However, it appeared not to be sufficiently attractive from an economic point of view to be implemented on an industrial scale in the new Roche plant in Scotland.

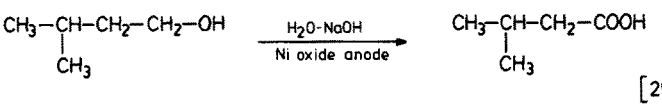
Merck studied the use of iron oxide anodes [289] for this reaction (yields up to 91%). The rapid loss of electrode activity can be suppressed by adding alkali-resistant solvents, such as anisole or xylene [290].

To improve the long-term stability of the common nickel oxide anodes, surfactants, such as substituted polyglycol ethers, are added to the electrolyte [291]. Merck has proposed a combined process (in which about 80% of the diacetonesorbose are oxidized electrochemically, and the remainder conventionally [292]) and a special procedure for the work-up procedure by electrodialysis (removal of the unconverted diacetonesorbose [293]). It is said that Merck is using the electrosynthesis of diacetoneketogulonic acid for the industrial production of vitamin C.

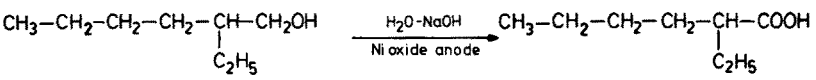
The method was also used for the laboratory synthesis of a number of other aliphatic carboxylic acids.



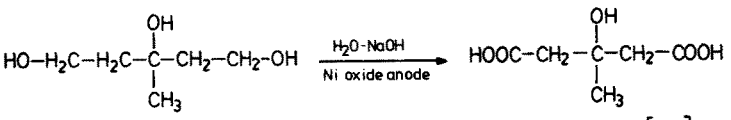
Yield: >95%
Current efficiency: 90% [294]



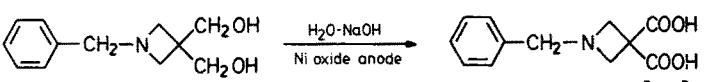
[295]



[296]

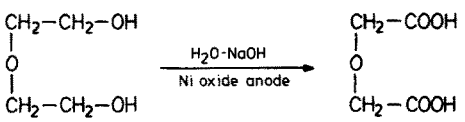


Yield: 70-85% [297]

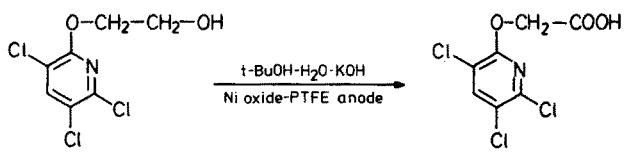


Yield: 70% [298]

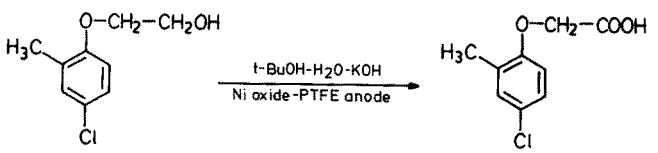
Dow has applied the reaction principle to the preparation of diglycolic acid [299-300] and phenoxyacetic acids [301] on the laboratory scale:



Yield: 75-88%
Current efficiency: 69-76%

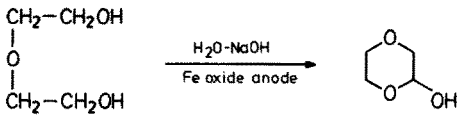


Selectivity: 97%
Current efficiency: 70%



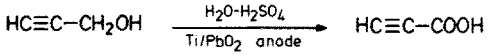
Selectivity: 97%
Current efficiency: 50%

The substituted phenoxyacetic acids are used as herbicides. If Fe oxide anodes are used in the electrochemical oxidation of diethylene glycol, 1,4-dioxan-2-ol is initially formed [302]:

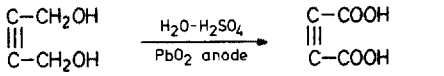


Conversion : 60 %
Yield : 51 %
Current efficiency : 39 %

On the other hand, acetylenic alcohols can be electrochemically converted to the corresponding acetylene carboxylic acids in acidic electrolytes using PbO_2 anodes. Processes for the synthesis of propynoic acid and acetylene dicarboxylic acid have been developed at BASF [303–304].

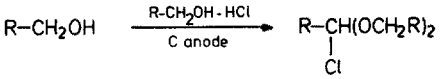


Yield : 76 %



Yield : ≥ 70 %

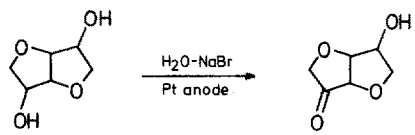
An interesting synthesis of 2-haloaldehyde acetals was discovered by Monsanto [305]:



R: $-CH_3$: Selectivity : 90 %
Current efficiency : 80 %
R: $n\text{-}C_3H_7$: Selectivity : 95 %
Current efficiency : 64–77 %

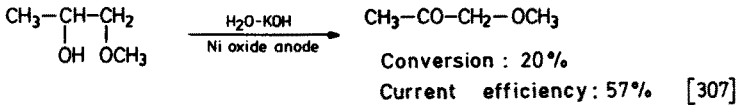
3.1.7.2 Electrosynthesis of Ketones

The anodic oxidation of secondary alcohols to the corresponding ketones is generally inferior to the catalytic dehydrogenation methods. Electrochemical syntheses are therefore of interest only in special cases. An example of this is the regioselective oxidation of an endo-hydroxyl group in 1,4,3,6-dianhydrohexitols [306]:



Selectivity : 80 %
Current efficiency : 50 %

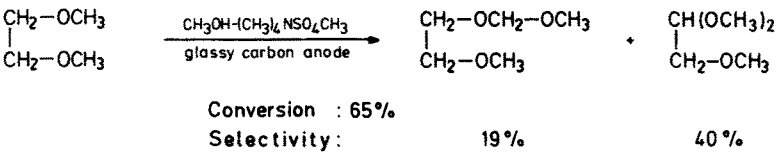
The nickel oxide anode can also be used in the oxidation of secondary alcohols but frequently has no advantage over catalytic processes:



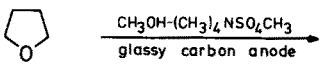
[307]

3.1.7.3 Anodic Oxidation of Aliphatic Ethers

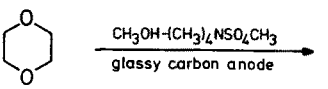
The electrochemical oxidation of aliphatic ethers is known from the literature and was investigated in more detail by Hoechst [308]. The use of glassy carbon anodes led to a considerable increase in the current efficiencies and extended the range of useful ethers.



Conversion : 65%
Selectivity: 19% 40%



Selectivity: 81 %
Current efficiency: 75 %

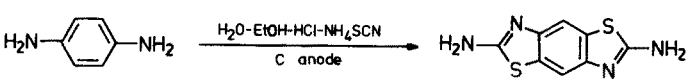


Selectivity : 82%
Current efficiency: 72 %

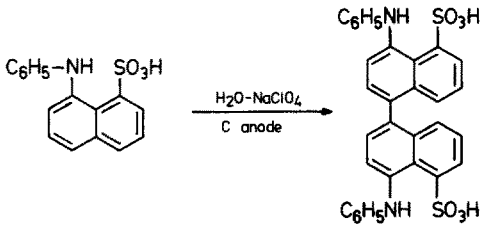
3.1.8 Anodic Oxidation of Nitrogen Compounds

The oxidation of amines is very well documented in the scientific literature. Little work has been done in this area in industry (patent literature) over the past few years, however. One reason for this is certainly the frequently unsatisfactory yields in these reactions.

Using *p*-phenylenediamine as a starting material, Celanese [309] attempted to produce new monomers for engineering plastics:

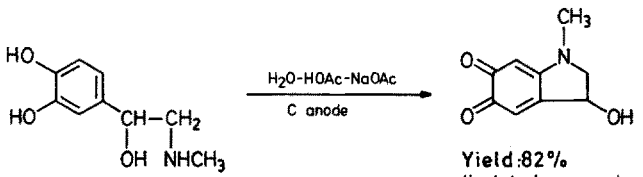


Substituted naphthylamine derivatives can be anodically dimerized [310]:



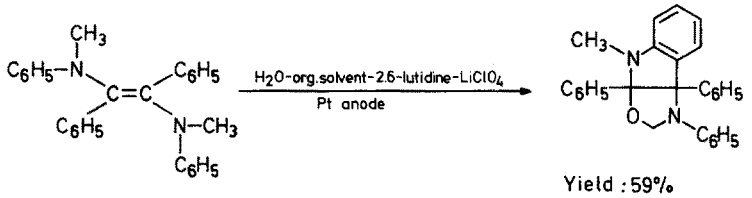
Conversion: 88 %
Yield : 30 %

Tanabe studied the anodic oxidation of adrenaline derivatives [311–312]:



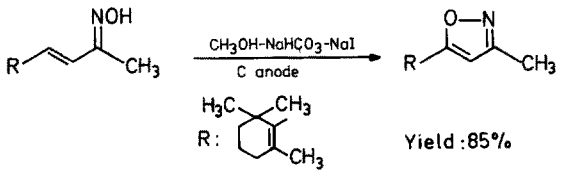
Yield:82%
(isolated as semicarbazone)

The oxidation of enamines [313] was used for the synthesis of potential drug intermediates:



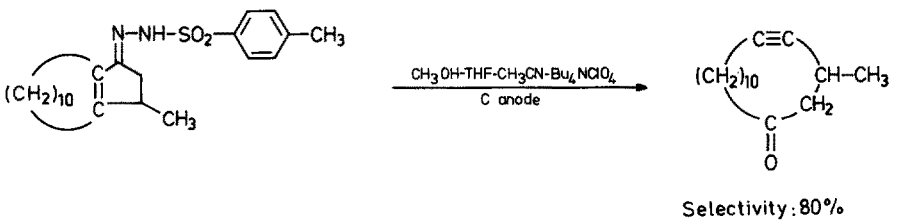
Yield : 59%

Oximes of α, β-unsaturated carbonyl compounds can be converted to isoxazoles in a smooth reaction [314]:



Yield : 85%

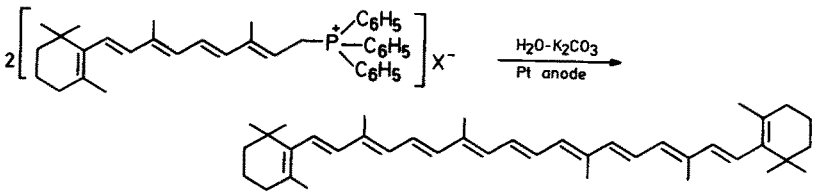
Firmenich [315] used the oxidation of hydrazones for a novel syntheses of musk fragrances:



Selectivity : 80%

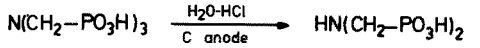
3.1.9 Anodic Oxidation of Phosphorus Compounds

The anodic oxidation of organic phosphorus compounds has been studied intensively over the past few years, especially in the USSR. The anodic oxidation of triphenylphosphine in the presence of aromatics or heterocycles, e.g. thiophene [316], gives the corresponding triphenylaryl- and triphenylhetarylphosphonium salts, respectively (yields for triphenylthienylphosphonium salt: up to 72%). The oxidation of dialkyl phosphites in the presence of aromatics gives aryl phosphonates [317-318] or allows the synthesis of tetraalkyl phosphonates [319]. The common feature of all syntheses is the use of aprotic electrolytes, e.g., $CH_3CN/NaClO_4$. Stauffer [320-321] used anodes of phosphorus (on a graphite carrier) or ferrophosphorus for the synthesis of phosphates, such as triethyl phosphate. The anodic oxidation of triphenylphosphonium salts is a possible method of C—C coupling, as demonstrated by a new BASF β-carotene synthesis [322]:



Selectivity: 58 %

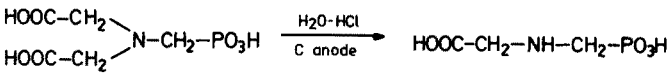
Monsanto [323] discovered electrochemical syntheses which permit the selective elimination of phosphonomethyl groups:



Yield: up to 91%

The reaction is generally applicable and is used for the synthesis of special metal ion sequestering agents:

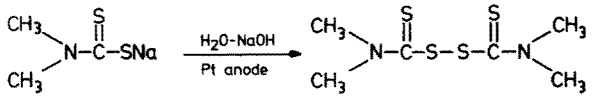
A laboratory-scale synthesis of N-phosphonomethylglycine was also developed [324].



Yields: up to 96 %

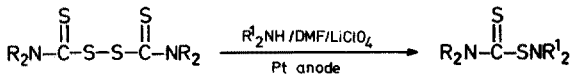
3.1.10 Anodic Oxidation of Sulfur Compounds

Industrial work has been concentrating on the search for alternative processes for the production of tetraalkylthiuram disulfides [325].



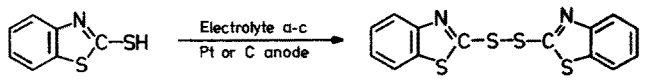
Conversion: 10-25%
Selectivity: 95%
Current efficiency: 88%

Their synthesis can also be carried out as a two-phase electrolysis, using ammonium salts [326]. Sulfenamides can be produced by oxidizing tetraalkylthiuram disulfides in the presence of amines [327]:

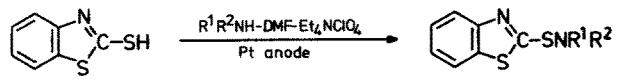


Tetraalkylthiuram disulfides are used as vulcanization enhancers, fungicides, and seed treatment agents. Commercial production is still performed by means of oxidation with Cl_2. Although their electrochemical synthesis avoids the production of NaCl, which is inevitable in the other processes, it is currently not being employed in industry.

The above reaction principle can be extended to the synthesis of dibenzothiazyl disulfide [328] and benzothiazolylsulfenamides [329].

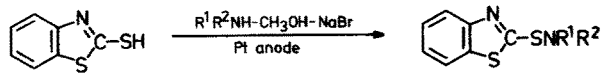


a: Et_3N-CH_3OH : Yield 99%
b: $CH_3OH-NaBr$: Yield 99%
c: H_2O-KOH : Yield 98%

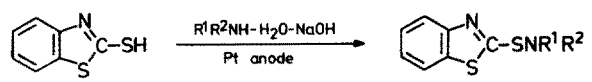


R^1 =  , R^2 = H: Yield 99%

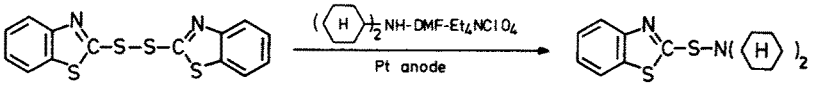
R^1 =  , R^2 = H: Yield 99%



$R^1 = R^2$ =  : Yield: 99%

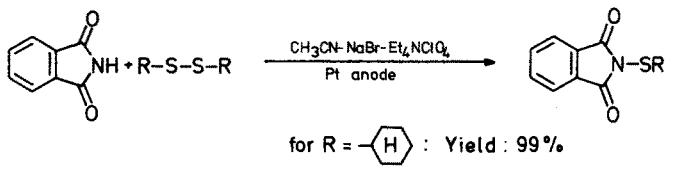


R^1 = t-C_4H_9–
R^2 = H Yield :99%

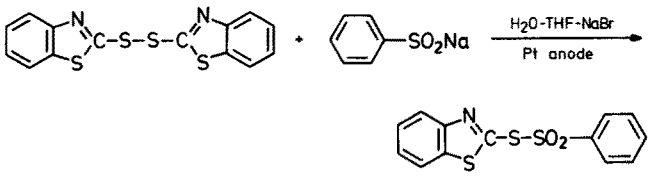


Yield 98%

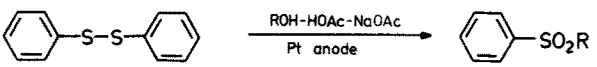
The anodic cleavage of disulfides was used on the laboratory scale for the synthesis of other vulcanization enhancers [330-331], for the production of phenyl sulfinates [332], and for the synthesis of intermediates for penicillins and cephalosporins [333].



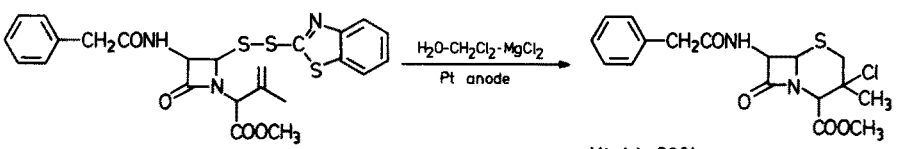
for R = H : Yield : 99%



Yield : 92%

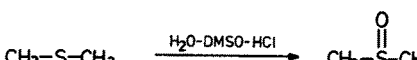


Yield: 74%

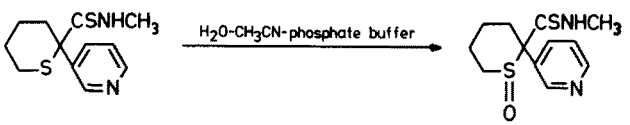


Yield : 93%

Apart from S—S coupling and cleavage reactions, attempts were made to find an electrosynthesis for sulfoxides (Enka [334-335] and Rhone-Poulenc [336]):



Selectivity : 91%
Current efficiency : 70%



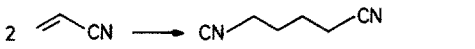
Yield : 73%

3.2 Cathodic Reduction

3.2.1 Reduction of C=C Double Bond Systems

3.2.1.1 Cathodic Hydrodimerization of Activated Olefins

From the industry's point of view the most important electroorganic reaction is the cathodic hydrodimerization of acrylonitrile to adipodinitrile. The basic work and scaling up of the process were carried out by Monsanto.



Selectivity: 90%
Current efficiency: 85%

Baizer [337] and Danly [338–341] wrote many detailed reports on the development of this synthesis from the early laboratory experiments to the production stage. The process was initially carried out in divided cells but was subsequently made much more cost-effective by changing over to undivided cells. Some important characteristic data of the two versions of the process [341] are summarized in the table below.

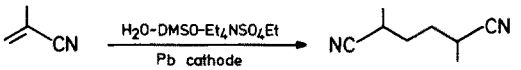
Electrosynthesis of adipodinitrile (ADN)

	divided cell	undivided cell
Cathode	Pb	Cd/steel
Anode	Pb (1% Ag)	Steel
Membrane	Ionics CR 61	—
Electrode gap (mm)	7	1.8–2.0
Electrolyte (wt %)	Et_4NSO_4Et (40)	$EtBu_2N(CH_2)_6$—NBu_2Et phosphate (0.4) Na_2HPO_4 (10) $Na_2B_4O_7$ (2) Na_4EDTA (0.5)
Current density (A/dm^2)	45	20
Energy consumption (kWh/kg ADN)	6.6	2.3

The process was also investigated by Asahi [342], BASF [343], Phillips [344], and others. It is now carried out industrially by Monsanto, Asahi, and BASF. Whereas Monsanto and BASF now use undivided cells in their industrial plants, Asahi [345] is still planning a changeover to undivided cells.

Adipodinitrile is an intermediate for hexamethylenediamine, the amine component of nylon 66. The electrochemical process is economically superior to the synthesis of adipodinitrile from cyclohexanone. Today, it essentially competes with the addition reaction of HCN to butadiene. The total capacity of the electrochemical ADN synthesis is currently about 250,000 tonnes/year. The process is industrially fully developed. Recent work [346–347] is aimed at reducing the oxygen evolution potential at the anode in order to save further energy.

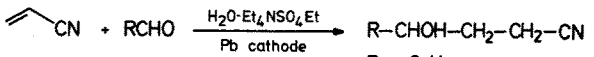
Methacrylonitrile can be subjected to a similar cathodic hydrodimerization reaction (Asahi [348-350]):



Selectivity: 82%
Current efficiency: 75%

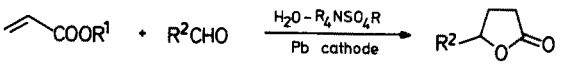
Maleic acid derivatives give 1,2,3,4-butanetetracarboxylic acid derivatives under similar conditions [351-352].

Activated olefins can also be subjected to cathodic C—C cross coupling reactions with carbonyl compounds. An example of this is the synthesis of γ-hydroxynitriles from acrylonitrile and aliphatic aldehydes [353]:

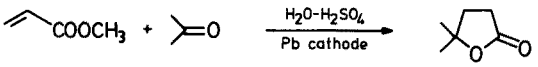


R: n-C_3H_7:
Yield: 20%, based on acrylonitrile

If an acrylate is used instead of acrylonitrile, the corresponding butyrolactones are obtained directly [354-360]:

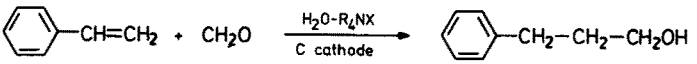


In the reaction with ketones [361-365], such as acetone, very good yields are obtained in some cases.

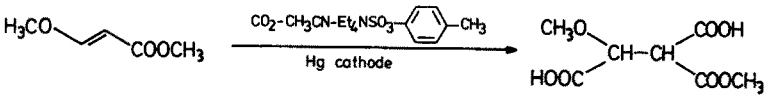


Selectivity: 91%
Current efficiency: 82%

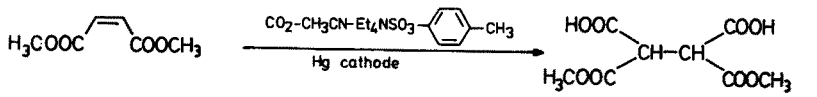
Butyrolactones are used in the synthesis of cyclopentenone derivatives [362,364]. 3-Phenyl-1-propanol can be produced from styrene and formaldehyde [366].



Activated olefins can also be cathodically carboxylated using CO_2 as electrophile:

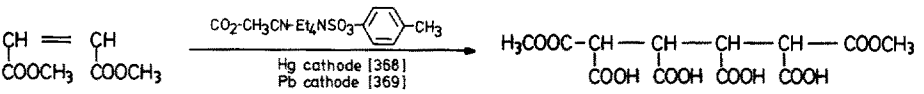


[367]

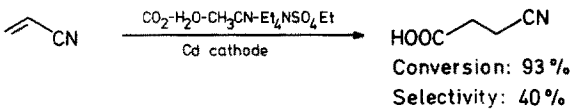


Current efficiency: 31%
[368]

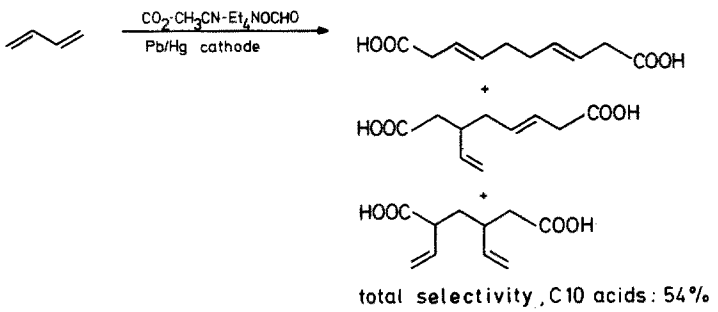
At higher olefin concentrations, additive dimerization of the olefin is also observed [368, 369]:



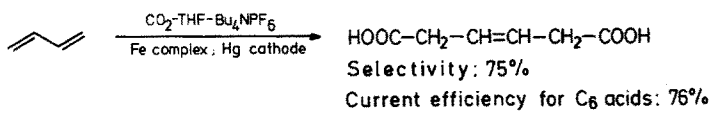
In this reaction CO_2 can be produced at the anode by anodic oxidation of oxalic acid derivatives [369]. In particular cases, the reaction can also be carried out in the presence of small amounts of water [370]:



Butadiene can also be carboxylated with CO_2 [371]:



In the presence of iron carbonyl complexes [372], the dimerization of the butadiene can be substantially suppressed:

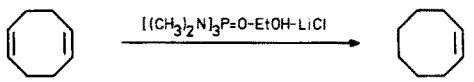


The work forms part of intensive efforts to find an adipic acid synthesis based on butadiene.

3.2.1.2 Cathodic Reduction of C—C Double and Triple Bonds

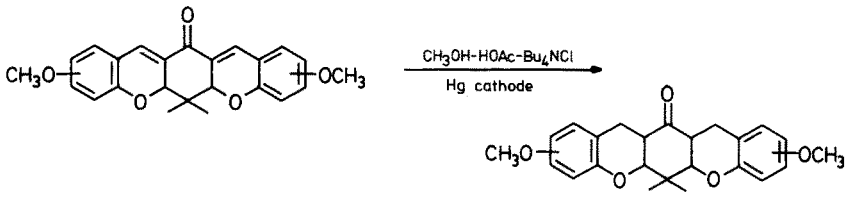
Work on the electrochemical reduction of C—C double and triple bonds is rarely encountered in the patent literature since these syntheses are generally not competitive with catalytic methods. Electrochemical processes are only of interest where particular selectivities may be obtained.

For example, Asahi [373] has investigated the cathodic reduction of alicyclic dienes:



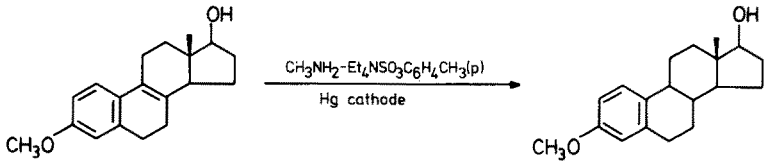
Conversion: 26%
Selectivity: 81%

Since the selective hydrogenation of only one double bond in dienes can also be carried out catalytically, this reduction will continue to be relatively unimportant even in the future. Lilly [374] has used the selective reduction of C=C double bonds in the presence of a carbonyl group for the synthesis of hexahydrobenzopyranoxanthenones (compounds with antiandrogen activity):



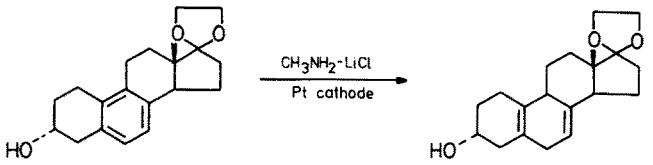
Yield: 85%

This method can also be used for steroid syntheses (Schering [375-376]):



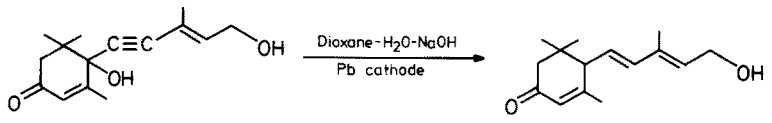
Yield: >95%

Acidic-alcoholic electrolytes may be used [377], but divided cells have to be employed in this case. In electrolytes consisting of amines and Li salts, the aromatic B ring in steroids can be converted selectively into the 9-α-H-dihydro compound [378]:



Yield: 95%

An example of the selective conversion of a C≡C triple bond into a C=C double bond was described by Roche [379] in connection with carotenoid syntheses:



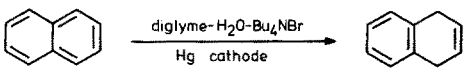
Conversion: 90%
Yield: 54%

3.2.1.3 Cathodic Reduction of Aromatics

The electrochemical reduction of aromatics to the corresponding 1,4-dihydro compounds can be performed by a procedure similar to the Birch reduction. It has been studied intensively in industry. Two different process modifications are to be distinguished:

a) Use of nonaqueous electrolytes; advantage: use of solid electrodes and Hg or amalgams may be avoided; disadvantage: poor conductivity of the electrolytes
b) Use of water-containing electrolytes, in particular in the presence of quaternary ammonium salts; advantage: favorable conductivity of the electrolytes; disadvantage: Hg or amalgam electrodes have to be employed and divided cells are to be used. Some of the results obtained in the electrochemical reduction of benzene to 1,4-cyclohexadiene are summarized in the table below.

This reaction principle was also extended to a number of substituted benzene derivatives [386, 390–391]. Thus, the reduction of *p*-xylene (Hg cathode, N-methylpyrrolidone-H_2O—Bu_4NBr electrolyte) yields 1,4-dimethylcyclohexadiene with a current efficiency of about 80% [393]. A number of papers have also been published on the reduction of naphthalene [394–397]:



Conversion: 99%
Selectivity: 92%
Current efficiency: 70% [394]

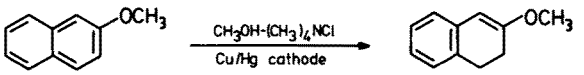
Electrosynthesis of 1,4-cyclohexadiene

Cell	Cathode	Catholyte (Electrolyte)	Conversion benzene (%)	Selectivity (%)	Current efficiency (%)	Ref.
Divided	Pt	$[(CH_3)_2N]_3P{=}O$ —CH_3OH (80/20)—LiCl	—	29	—	380)
Undivided	C	EDA-H_2O (40/75)— HCl-ethylhexadecyl-dimethylammonium bromide	26	96	79	381)
Undivided	C	EDA-BF_3-NH_4Cl	20	86	60	382)
Undivided	Pt	NH_3—NaCl	55	98	25	383)
Undivided	Al	NH_3—CH_3OH (3%) —NaCl	55	98	40	384)
Divided	Al	$[(CH_3)_2N]_3P{=}O$— n-PrOH—LiCl	5	98	67	385)
Divided	Hg	diglyme-H_2O—Bu_4NBr	38	96	52	386)
Divided	Hg	diglyme-H_2O—Bu_4NBr	—	—	81	387)
Divided	Hg	trioxane-H_2O—Bu_4NBr	—	95	80	388)
Divided	Cu/Hg	H_2O—Bu_4NBr	—	92	81	389)
Divided	Hg	H_2O—$(Bu_4N)_2SO_4$— Bu_4NOH	—	93	67	390)
Undivided	Hg	H_2O—Bu_4NOH	—	92	—	391)
Divided	Zn/Hg	Diethylene glycol-Bu_4NBr	43	91	74	392)

EDA: ethylenediamine

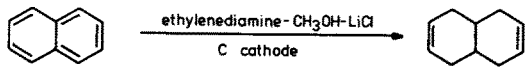
Experiments using Pb cathodes in an undivided cell (NH_3 oxidation as the anode process) indicate rapid deactivation of the cathodes. By optimizing the electrolyte, the operating times can be increased to about 40 hours without deactivation [395]. However, this operating time is still far from sufficient from the industrial point of view.

The reduction of alkoxynaphthalenes [398] was used by Hoechst for the synthesis of β-tetralones:



Yield: 95 % of dihydro derivative; including 80% of the 3.4-dihydro compound

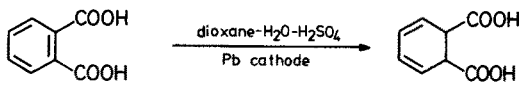
An electrochemical method can also be used for the reduction of both rings of the naphthalene system [399]:



Yield : 85 %

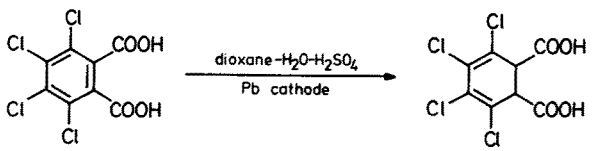
The dihydroaromatics, in particular 1,4-dihydrobenzene, were intended for use as comonomers for special polymers. However, since these polymers are not used industrially, the electrosyntheses have not been applied industrially as well.

Because of their more positive cathode potentials, phthalic acid derivatives are considerably easier to reduce. 1,2-Dihydrophthalic acid [400] was produced industrially by BASF for many years by electrochemical reduction of phthalic acid:



Yield : 94%
Current efficiency : 70%
Energy consumption: 4.3 kWh/kg

The reaction conditions can also be used for substituted phthalic acids [401]:

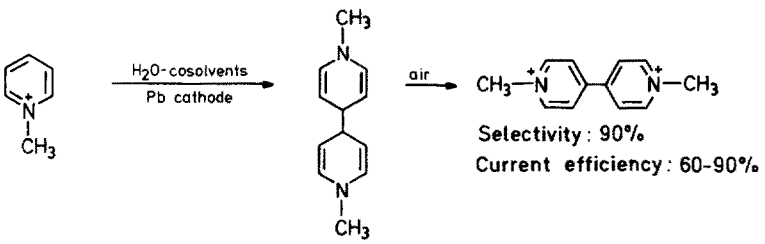


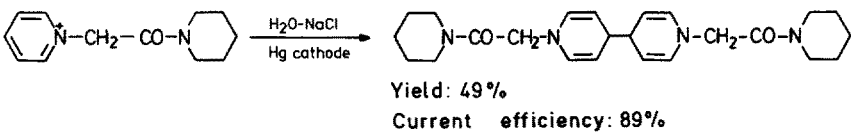
Yield : 98%
Current efficiency: 78%

3.2.1.4 Cathodic Reduction of Heterocycles

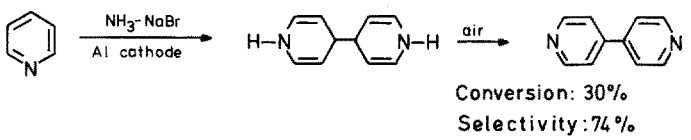
From the industry's point of view the most important reaction in this area is the electrosynthesis of bipyridyls from N-substituted pyridinium salts. The products are used as

herbicides. The reaction was investigated in particular by ICI [402-403] and Asahi [404-407].

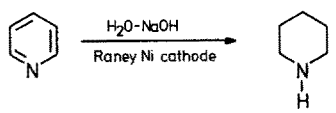


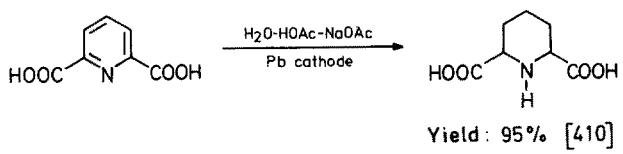


The electrochemical reduction is in competition with the reduction by sodium in liquid ammonia. The electrosynthesis can also be carried out under Birch conditions [408]:

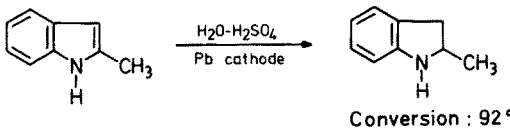


In aqueous electrolytes pyridines can be converted to the corresponding piperidines, although the processes are generally inferior to catalytic hydrogenation:

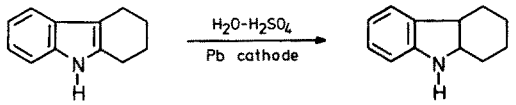




The electrochemical reduction of indole derivatives [411-413] and tetrahydrocarbazole [413] has been carried out industrially. The reduction products have been required as dye intermediates.

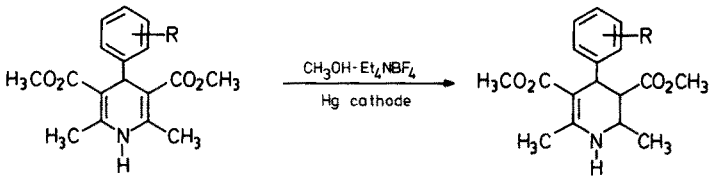


Conversion : 92 %
Yield : 91 %
Current efficiency : 46 %



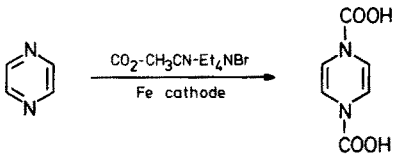
Conversion : 94 %
Yield : 99 %
Current efficiency : 55 %

Specially substituted tetrahydropyridine derivatives with a coronary dilatory action were produced by electrochemical reduction of the corresponding dihydropyridines[414].



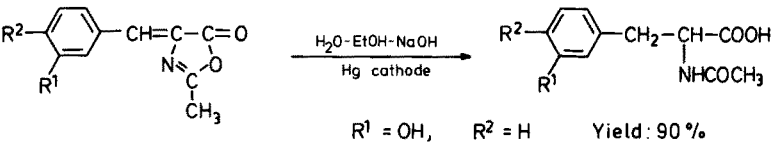
R=H : Yield : 39 %
R=2-Cl : Yield : 54 %
R=4-Cl : Yield : 62 %
R=2-CH_3O : Yield : 67 %

In aprotic electrolytes, diazaheterocycles can be reductively carboxylated at the nitrogen atoms[415]:



Selectivity : 78 %
Current efficiency : 75 %

The electrochemical reduction of oxazolones was used for the synthesis of substituted phenylalanines[416]:

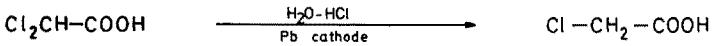


R^1 = OH, R^2 = H Yield : 90 %
R^1 = OCH_3, R^2 = H Yield : 75 %
R^1 = OCH_3, R^2 = OCH_3 Yield : 69 %
R^1 = OCH_3, R^2 = OH Yield : 80 %

3.2.2 Reduction of Organic Halogen Compounds

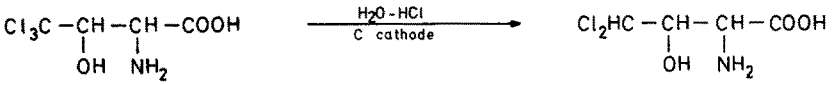
3.2.2.1 Cathodic Reduction of Aliphatic Halogen Compounds

The electrochemical cleavage of C-halogen bonds allows to remove one halogen atom from polyhalogenated compounds selectively, to introduce C=C double bonds, and to produce organometallic compounds. Some examples from the patent literature are summarized below:



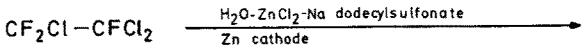
[417]

The reaction can be used for recycling more highly chlorinated acetic acids in the production of monochloroacetic acid.

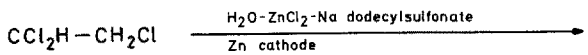


Yield: 82% [418]

R: –COOH, yield: 85%
current efficiency: 72%
R: –CN, yield: 91%
R: $-CONH_2$, yield: 88%
[419]

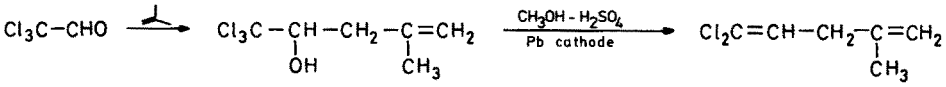


Selectivity: 90%
Current efficiency: 82%
[420]

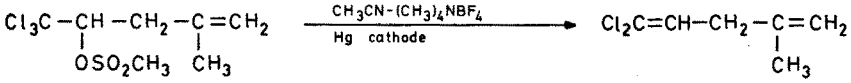


Selectivity: 98%
Current efficiency: 99%
[420]

ICI [421] and FMC [422] have used this reaction for the synthesis of a key intermediate for pyrethroids:

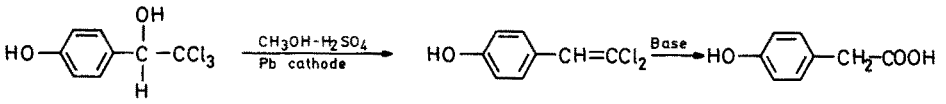


Yields not specified [421]



Yield: 81% [422]

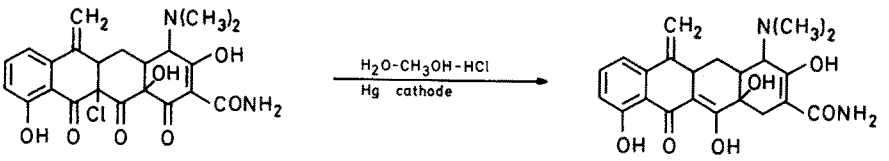
Trichloromethylcarbinols can be used as intermediates for new phenylacetic acid syntheses [423]:



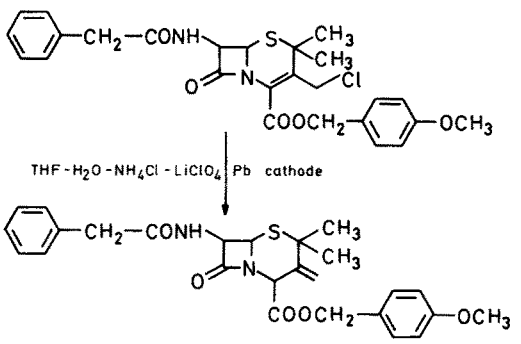
Yield: 97%

However, the synthesis is inferior to the processes based on phenols and glyoxylic acid. One reason is the large amount of waste salts which are inevitably produced.

Reductive dehalogenation has been used for the synthesis of antibiotics



Yield: 95%
[424]



Yield: 87%
[425]

and for the destruction of hexachlorocyclohexane-containing residues (reduction to benzene [426]).

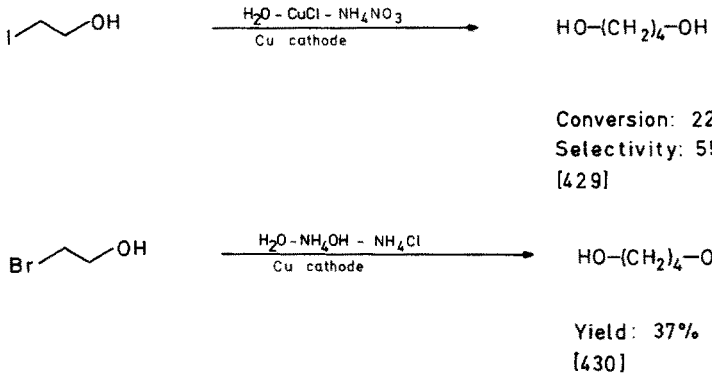
In aprotic catholytes, the cathodic reduction of alkyl halides at Sn cathodes leads to organotin compounds [427-428]:

$$n\text{-}C_4H_9Cl \xrightarrow[\text{Sn cathode}]{CH_3CN\text{-}Et_4NCl} (C_4H_9)_3SnCl$$

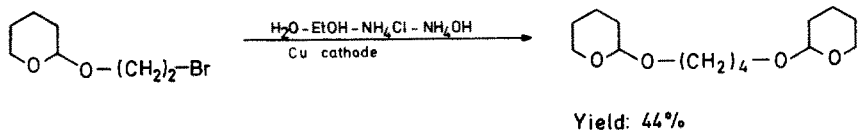
In the presence of air, dibutyltin oxide is formed. The compounds are used as vulcanizing agents and stabilizers for plastics.

3.2.2.2 C—C Coupling by Reductive Dehalogenation

Reductive dehalogenation can also be used for C—C coupling. New syntheses for 1,4-butanediol are of industrial interest.

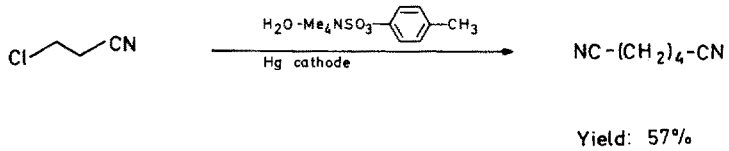


An application by Asahi [431] states that the addition of basic heterocycles (e.g., bipyridine, imidazole or 1,2,4-triazole) is advantageous. Better yields are obtained if the hydroxyl functions are protected as ethers [432].



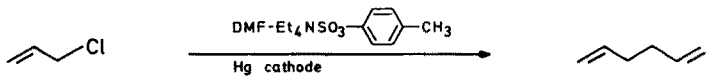
The new syntheses cannot compete with the established processes based on acetylene and formaldehyde, not least because the yields are still not very satisfactory.

Adipodinitrile also can be obtained by reductive dehalogenation [433].

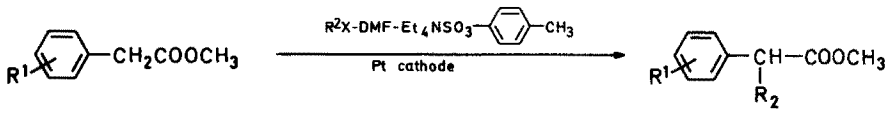


However, the synthesis cannot compete with the cathodic hydrodimerization of acrylonitrile.

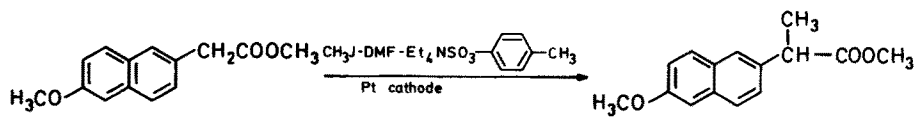
If the C—C coupling reactions are carried out in aprotic electrolytes, the yields and selectivities can be increased, in some cases considerably. Some examples which are also of industrial interest are given below:



Conversion: 38 %
Selectivity: 75 %
[434]



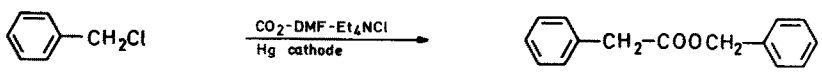
R^1=H, R^2=i-C_3H_7, X = Br: Yield: 80 %
R^1=4-OCH_3, R^2=-CH_3, X = I : Yield: 85 %
R^1=4-i-C_4H_9, R^2=-CH_3, X = I : Yield: 82 %
[435]



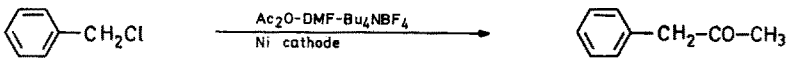
Yield: 82 % [435]

The cathodic dehalogenation can be carried out by an indirect route; for example, by reducing aromatic azo compounds [436–439].

Phenylacetic acid derivatives [440–441] and phenylacetone [442] can be obtained by carboxylation respectively acetylation of benzyl chloride.

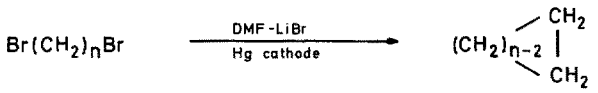


Yield: 78 %
Current efficiency: 40 %



Conversion: 64%
Selectivity: 84%
Current efficiency: 49%

Finally, reductive dehalogenation was also used for the synthesis of small rings [443]:

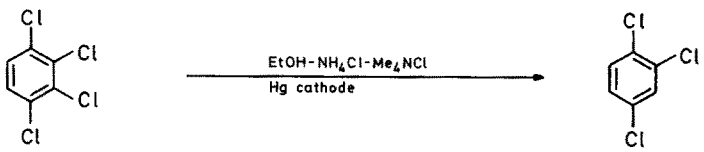


n = 3: Yield: 85%
n = 4: Yield: 25%

The possibility of carrying out C—C coupling via reductive dehalogenation would in many cases be an interesting alternative to existing methods in industrial applications. However, during scale up fundamental problems arise. Particularly in those examples which are of industrial interest, the aprotic conditions must be stringently observed. Thus, even at high conductive salt concentrations, the electrolytes still have relatively low conductivities. For these conditions, however, there is no industrially suitable divided cell. One approach to solve this problem is to carry out the reactions in undivided cells using sacrificial anodes (Al or Mg anodes) [444–445]. But this method too, is not a solution for industrial quantities. As long as these fundamental problems remain unsolved, these reactions of preparative interest are unlikely to be used industrially.

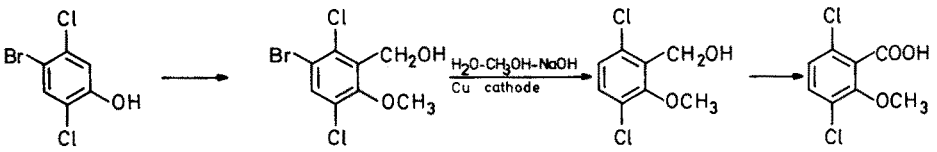
3.2.2.3 Cathodic Reduction of Aromatic and Heterocyclic Halogen Compounds

Aromatic halogen derivatives with unusual substitution patterns, which are otherwise difficult to obtain, can be prepared by electrochemical reduction of perhalogenated aromatics and heterocyclic compounds.



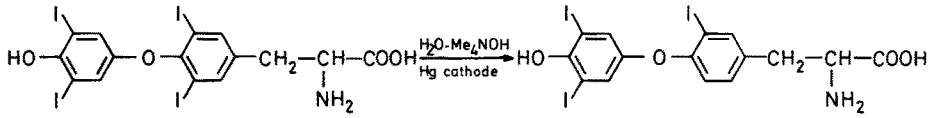
Conversion: 66%
Selectivity: 97%
Current efficiency: 71%
[446]

The reaction was used for the synthesis of herbicides [447-448]:



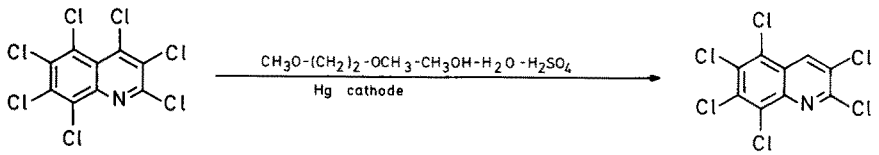
Yield: 96%

The regioselective monodehalogenation reaction has been described in connection with the synthesis of antithyroside drugs [449]:

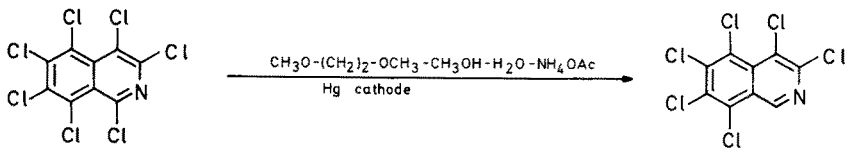


Yield: >99%

The cathodic removal of one halogen radical from perhalogenated quinolines and isoquinolines [450] occurs with high selectivity:

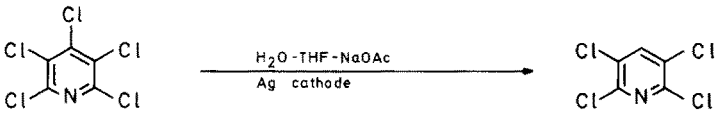


Conversion: 96%
Selectivity: 87%

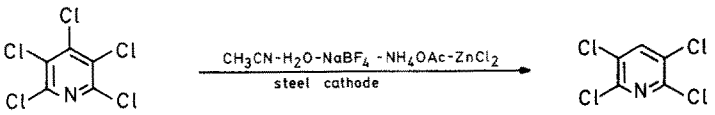


Conversion: 83%
Selectivity: 73%

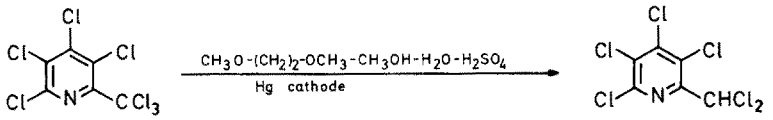
This method can also be used on perhalogenated pyridines [451–453]:



Selectivity: 94% [451]

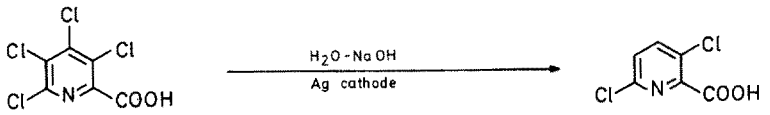


Conversion: 94%
Selectivity: >98%
Current efficiency: 25 - 65% (depending on cosolvent) [452]



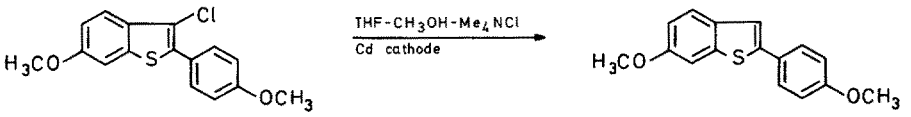
Conversion: 95%
Selectivity: 83% [453]

Dow has studied the reaction principle intensively for the synthesis of the herbicide 3,6-dichloropicolinic acid [454–458]:

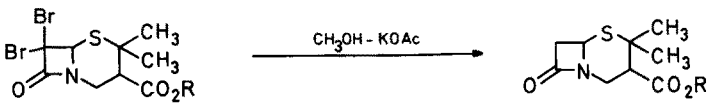


Yield up to 99%

Other applications of this method were reported by Lilly [459] and Kanebo [460]:



Yield: 91%
Current efficiency: 85%

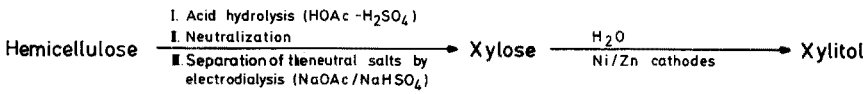


Yield: 75%

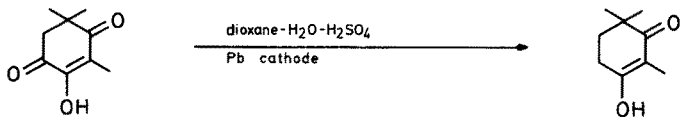
3.2.3 Reduction of Carbonyl Compounds and Derivatives

3.2.3.1 Aldehydes and Ketones

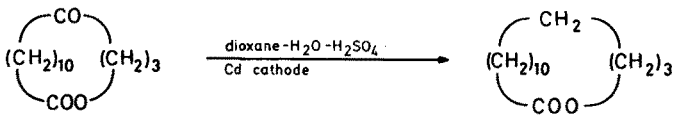
Even for the reduction of carbonyl compounds to the corresponding hydroxy derivatives, electrochemical processes are generally inferior to the catalytic syntheses from an economic point of view. Thus, sorbitol and mannitol were previously produced by electrochemical reduction of the corresponding aldoses [461]. These processes are no longer of industrial importance today. However, the electrochemical hydrogenation of sugar is once again attracting attention in conjunction with electrodialysis processes [462]:



Of greater industrial interest is the possibility of converting carbonyl compounds into the corresponding hydrocarbons. The reaction requires strongly acidic electrolytes. Examples of this reaction are syntheses in the areas of carotenoids [463] and fragrances [464]:

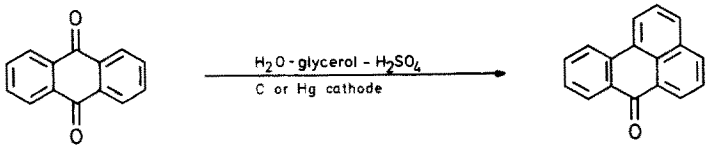


Yield: 82%



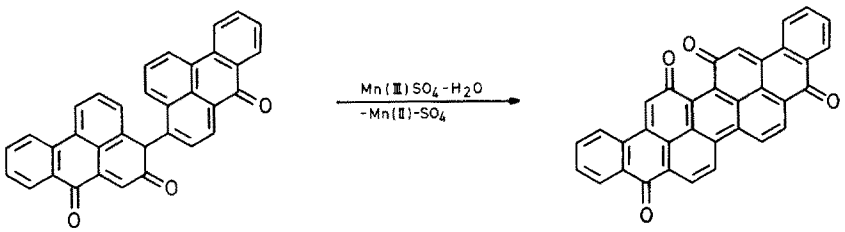
Conversion: 78%
Selectivity: 90%

The electrochemical reduction of carbonyl compounds can also be used for C—C coupling. An example of industrial interest is a new benzanthrone synthesis patented by Ciba [465]. If anthraquinone is reduced in 85% H_2SO_4 in the presence of glycerol, the oxanthrone formed as an intermediate reacts with glycerol to form benzanthrone:

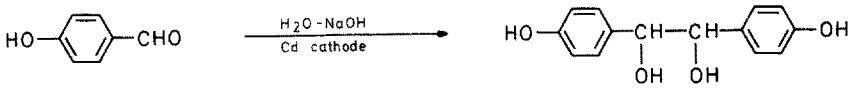


Yield: 85%

Since the reaction has to be carried out in a divided cell, the anode compartment can be used for a second reaction, for example, the oxidation of Mn(II) to Mn(III) sulfate [466]. The Mn(III) solution can then be used for the synthesis of dioxoviolanthrone (intermediate for vat dyes).



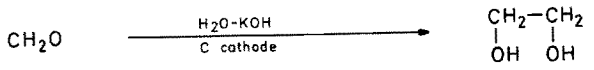
The electrochemical hydrodimerization of aromatic aldehydes is more familiar. The essential advantage of this electrosynthesis is the possibility to dispense with the use of metals as reducing agents. The reaction was investigated, for example, by Monsanto for the electrosynthesis of 1,2-bis-(hydroxyphenyl)-ethanediol [467–469]:



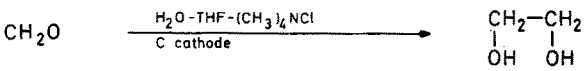
Conversion: 97%
Selectivity: 78%
Antioxidant

The use of a basic electrolyte makes it possible to employ undivided cells.

The cathodic hydrodimerization of aliphatic aldehydes, in particular of formaldehyde, could become more important industrially.

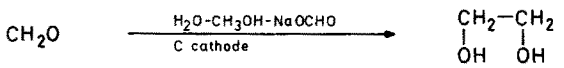


Selectivity: 94%
Current efficiency: 80% [470]



Current efficiency: 93% [471]

The addition of methanol or of quaternary ammonium salts to the electrolyte is said to increase the current efficiencies, even when weakly acidic electrolytes are used [472-473].

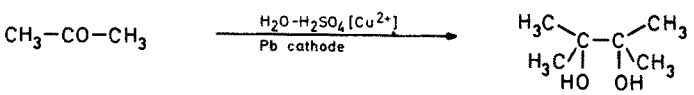


Current efficiency: > 90%

In a process proposed in a recent application by Texaco [474], methanol is anodically oxidized to formaldehyde, which is then reduced cathodically to glycol in the same cell.

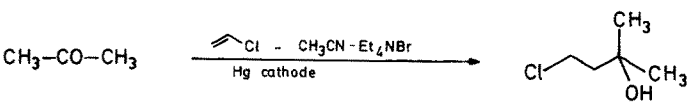
Today, ethylene glycol is produced worldwide from ethylene. A glycol synthesis based on C1 building blocks would become commercially interesting in case of a shortage of petrochemical raw materials or if they were to become more expensive. The electrosynthesis of glycol from formaldehyde would then compete with a high-pressure synthesis based on synthesis gas. A cost comparison based on experimental results to date shows that the electrosynthesis would have good prospects if it were possible to work up the electrolyte in a simple manner.

The cathodic hydrodimerization of acetone to pinacol is one of the most thoroughly investigated electrosyntheses of this class of reactions. Recent investigations indicate that the addition of small amounts of Cu^{2+} ions to the catholyte results in a substantial increase in the current efficiencies [475]:

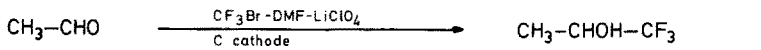


Current efficiency: up to 78%

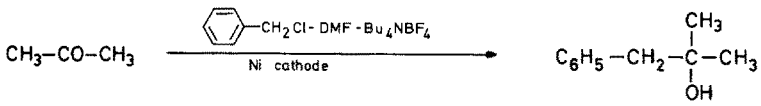
Carbonyl compounds can undergo cross-coupling reactions with olefins [cf. 3.2.1.1] and halogen compounds, for example, with vinyl chloride [476] and CF_3Br [477].



Selectivity: 52%



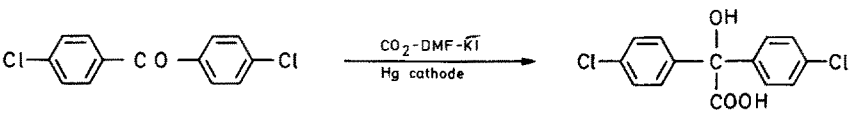
Current efficiency: 35%



Yield: 55-75% [478]

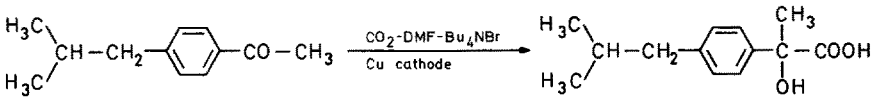
Also, in these reactions it is advisable to use sacrificial anodes (Al or Mg) [478].

Reactions with CO_2 in aprotic electrolytes lead to hydroxy acids. These reactions may be regarded as an alternative to Grignard syntheses with CO_2:



Yield: 90% [479]

This reaction was studied more intensively for the carboxylation of 4-isobutylacetophenone [480–484]:



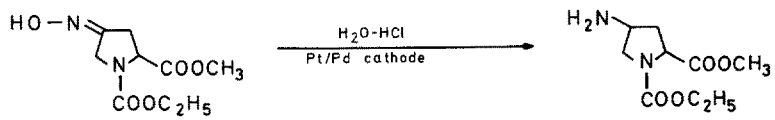
Yield: up to 90%
Current efficiency: up to 80%

The reduction of substituted 2-hydroxypropionic acid gives ibuprofen (antiinflammatory agent) in a simple manner.

However, if this reaction, which is of preparative interest, is to be scaled up to the industrial scale, the problems described in Sect. 3.2.2.2 first have to be solved.

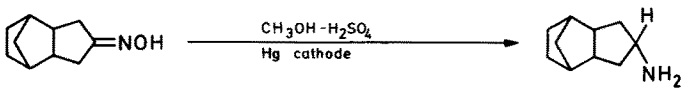
3.2.3.2 Compounds with C=N Double Bonds

Oximes can be converted electrochemically to the corresponding amino compounds in a smooth reaction. However, apart from a few examples, the electrosyntheses are inferior to catalytic reductions, so that only a few examples are described in the patent literature.



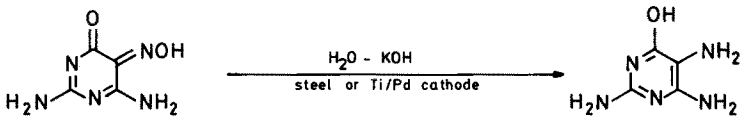
Yield: 78% [485]

The stereoselective reduction of a tricyclodecyl oxime has been described [486]:



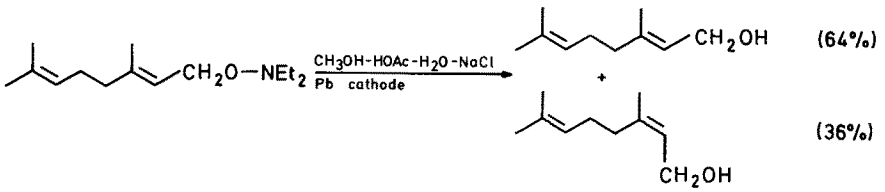
Yield: 89 %
endo form: ≥98%
Drug intermediates

Specially substituted pyrimidine derivatives [487-488] are also readily obtainable:



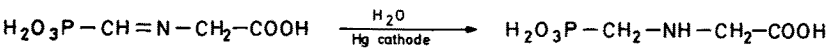
Yield: 96-98%
Current efficiency: 94-96%

Hydroxylamines can be reduced electrochemically with N—O bond cleavage. This reaction was used in a geraniol synthesis (fragrance material):



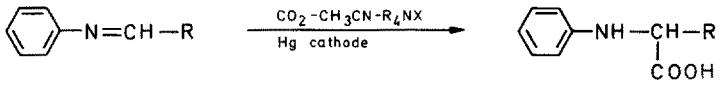
Current efficiency: 67%

Imines are electrochemically reduced to amines. An example of this is the synthesis of N-phosphonomethylglycine (herbicide) [490-491].



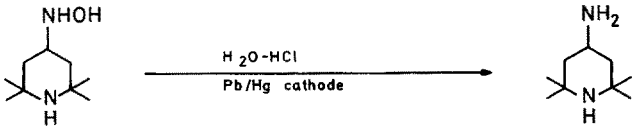
Yield: 65%

The reduction of benzylideneanilines in aprotic electrolytes in the presence of CO_2 can be used for the synthesis of N-phenylglycines [492-496]:

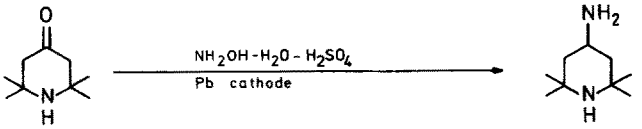


Yield: about 50%

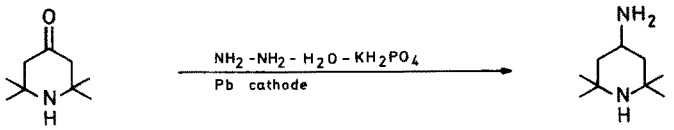
The electrosynthesis of 4-aminotetramethylpiperidine (used as a stabilizer for polymers) has been studied intensively, in particular in the USSR:



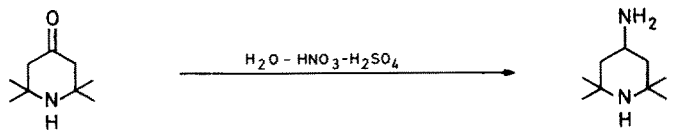
Yield: 77% [497]
Current efficiency: 55%



Yield: 84-99% [498]
Current efficiency: 50-83%



Yield: 98-99%
Current efficiency: 62-97%
[499-500]



Yield: 99%
Current efficiency: 23%
[501]

3.2.3.3 Carboxylic Acids

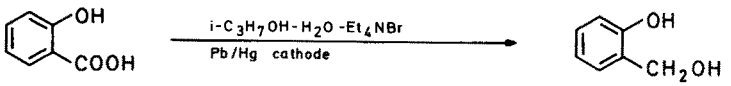
Also in the cathodic reduction of carboxylic acids, electrolysis is in competition with catalytic methods. However, catalytic hydrogenations in this area do not always proceed so smoothly that electrochemical processes are without any prospects from the outset.

Aromatic carboxylic acids, e.g., benzoic acid, can be electrochemically reduced to benzyl alcohols:

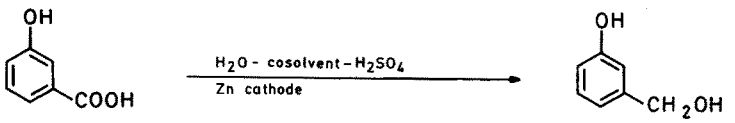
Conversion: 78%
Ratio of alcohol to aldehyde: about 5:1
Total current efficiency: 53%
[502]

Benzyl alcohol, on the other hand, is produced industrially from benzaldehyde or benzyl chloride, which are available economically in large amounts.

Better results are obtained in the reduction of *o*- and *m*-hydroxybenzoic acid:

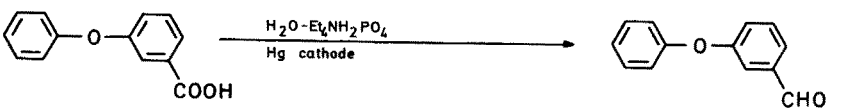


Selectivity: 79%
Current efficiency: 45-58% [503]
Intermediate for fragrances



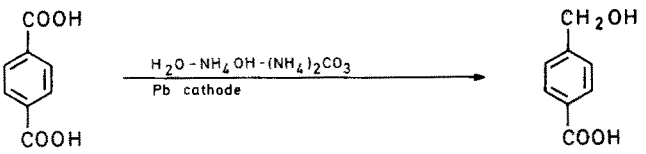
Yield: 94%
Current efficiency: 61%[504-505]

Sumitomo [506] has described the electrosynthesis of *m*-phenoxybenzaldehyde in a patent application:



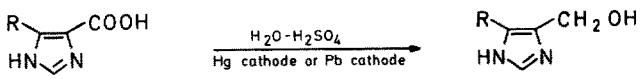
Selectivity: 93%
Current efficiency: 77%
Intermediate for insecticides

Terephthalic acid can be reduced smoothly to 4-hydroxymethylbenzoic acid (potential intermediate for polyesters) in alkaline electrolytes:



Conversion: quantitative
Yield: 80 %
Current efficiency: 48 %
[507]

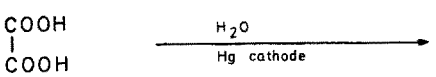
The activity of the lead cathodes is maintained by periodic short-circuiting. The reaction has been intensively investigated by Standard Oil [508 – 511] over the past few years. When Hg and Pb/Hg cathodes are used, the yields and current efficiencies can be increased to above 90 %. Heteroaromatic carboxylic acids can likewise be converted into the corresponding alcohols:



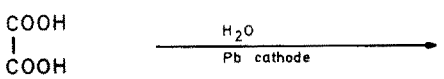
R: H or CH_3

Yield: 86 % [512]
Intermediates for drugs

Industrial work on the reduction of carboxylic acids was focused on the search for an electrochemical synthesis of glyoxylic acid from oxalic acid:



Conversion: 97 %
Yield: 85 %
Current efficiency: 97 % [513]



Conversion: 67 - 70 %
Selectivity: 93 - 98 %
Current efficiency: 75 - 97 %
[514 - 515]

The addition of small amounts of amines and ammonium salts makes it possible to increase selectivities and current efficiencies to about 90% over a prolonged period, even at Pb cathodes [516-517]. Recent Japanese applications claim special process modifications, such as the reactivation of the cathodes by pole reversal in alkaline electrolytes [518], special temperature programs during electrolysis [519], and working up the discharged electrolysis solution by electrodialysis methods [520]. The use of porous cathodes [521] was also proposed.

If the porous carbon cathodes are coated with copper or rhenium and an NH_4Cl-containing electrolyte is used, glycol aldehyde is obtained in the reduction of oxalic acid [522].

Glyoxylic acid is produced industrially in a fairly small amount by electrochemical reduction of oxalic acid. However, by far the major part is produced by oxidation of acetaldehyde (for example, with HNO_3) in a coupled production with glyoxal.

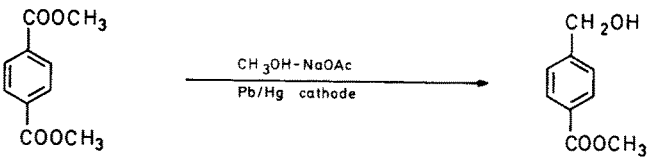
CO_2 can be reduced to oxalic acid in aprotic electrolytes in virtually quantitative yields and current efficiencies up to 90% or higher [523-528]. However, the necessity of using a divided cell and the exclusion of protic electrolytes make the process uneconomical. In aqueous electrolytes, CO_2 is reduced to formic acid [529].

The electrochemical reduction of CO yields squaric acid. The use of nitriles as solvents allows to increase the current efficiencies substantially [530]:

Current efficiencies up to 50 %

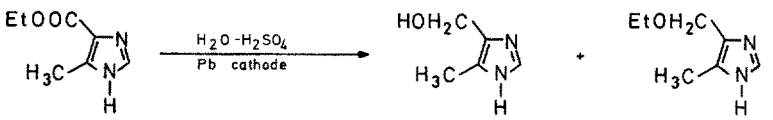
3.2.3.4 Carboxylates

Aromatic and heteroaromatic esters can be electrochemically reduced to benzyl alcohols, similar to the carboxylic acids. One example is the cathodic reduction of dimethyl terephthalate [531].



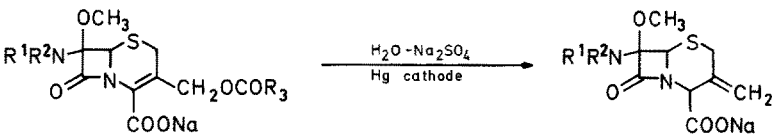
Conversion: 98%
Yield: 94%
Current efficiency: 85%
Intermediate for polyesters

The electrochemical reduction of imidazolecarboxylates gives a mixture (about 1:1) of ethers and alcohols when strongly acidic electrolytes are used [532]:

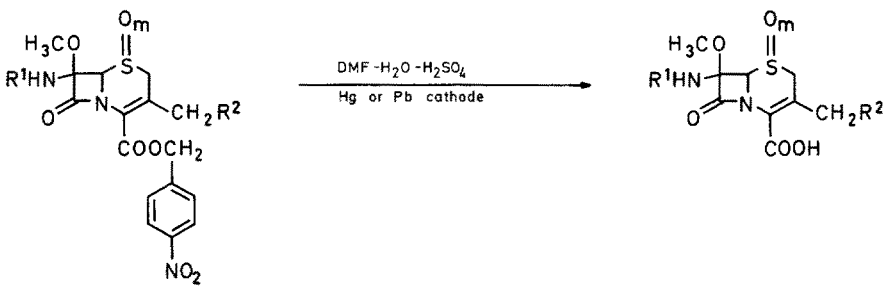


Total yield: 80%
Drug intermediates

Oxalates can be reduced to glyoxylates [533], in analogy to the oxalic acid reduction. Ester reductions have also been used for syntheses of cephalosporins [534-535].



Yield: 80%

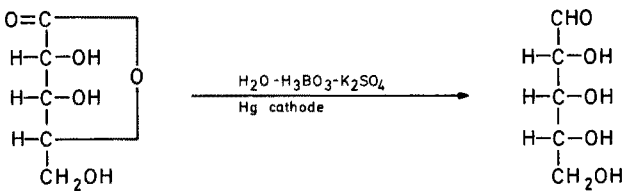


m = 0 or 1

Hydroxymandelates are electrochemically reduced to phenylacetic acid derivatives [536]:

$R^1 = R^2 =$ H or alkyl

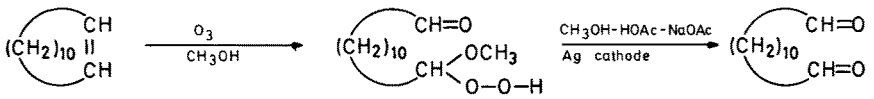
The reduction of lactones, e.g., ribonolactone [537-540], can be carried out over a prolonged period with reasonable current efficiencies only at Hg cathodes:



Yields: up to 87%
Current efficiency: 30-40%

This synthesis is carried out industrially for the production of vitamin B_2.

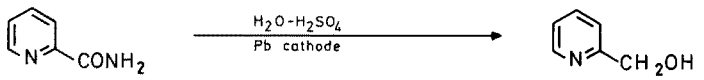
The alkoxyhydroperoxides, which are formed in the ozonolysis of olefins in alcohols, are electrochemically reduced to dialdehydes in very good yields [541-542]:



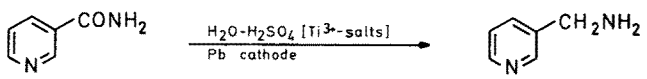
Yield: 87%

3.2.3.5 Carboxamides

Carboxamides can be cathodically reduced to amines or alcohols, depending on the reaction conditions; the reaction is carried out industrially. One example is the reduction of pyridine carboxamides at Reilly [543]:

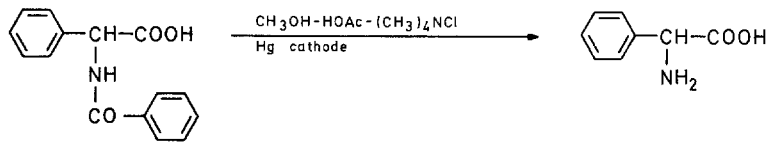


Conversion: 95%
Yield: 86%
[544]

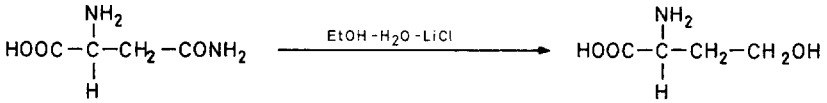


Yield: 75% [544]

The reaction can also be used for the stereoselective elimination of protective groups [545] and for the synthesis of amino acid derivatives [546]:

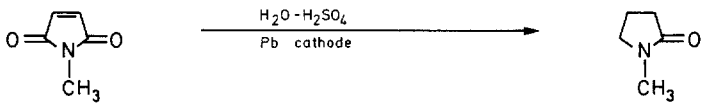


Yield: 80%
Optical purity: >98%
Intermediate for semisynthetic penicillins

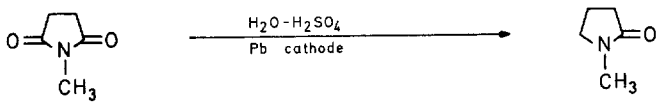


Yield: 71%

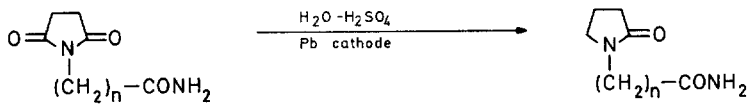
The electrochemical reduction of cyclic imides requires strongly acidic electrolytes, for example, a large excess of H_2SO_4. This leads to large amounts of waste salts during the isolation of the reduction products:



Conversion: 72%
Selectivity: 78% [547]

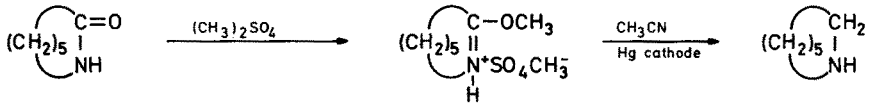


Yield: 83% [548]



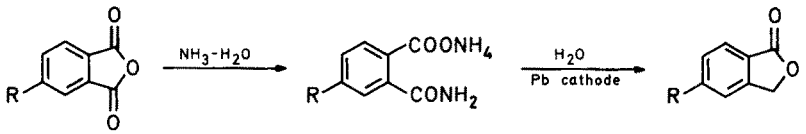
for n=1: Yield: 72%
Drug intermediates
[549-550]

If lactams are initially converted to the corresponding lactim ethers, the inevitable production of waste salts can be substantially reduced:



Conversion: 90%
Selectivity: 72% [551]
Intermediate for herbicides

On the other hand, the reduction of phthalic anhydride to phthalide is simpler. The key step in this synthesis is the electrochemical reduction of ammonium phthalamates [552-554].

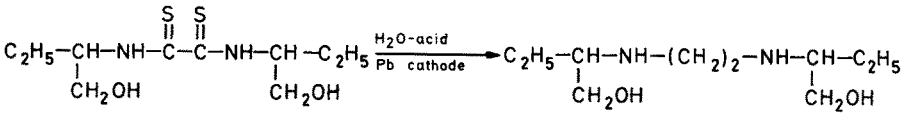


R: – H Conversion: 90%
Selectivity: 96%
Current efficiency: 73%

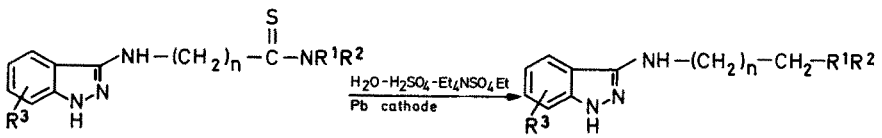
R: – COOH Conversion: 100%
Yield: 89%

Intermediate for drugs and dyes

Thioamides can be electrochemically reduced with cleavage of the C—S bond. The reaction was used for the synthesis of intermediates for auxiliaries [555] and drugs [556].



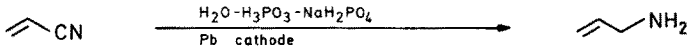
Yield: 85%



Yield: up to 96%

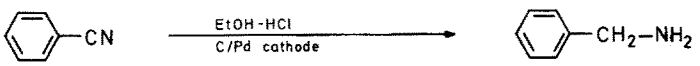
3.2.3.6 Nitriles

Like amides, nitriles can be reduced to amines or alcohols, depending on the reaction conditions. However, catalytic processes are generally superior to the electrosyntheses. The reduction of acrylonitrile to allylamine [557-558] is an exception:

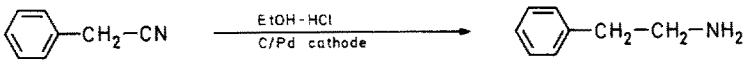


Yield: 85%

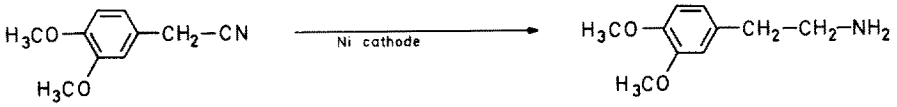
However, the electrochemical reduction requires a large excess of acids, which produce waste salts during work up and product isolation. This is certainly one of the reasons why the process has so far not competed successfully with the industrial syntheses based on allyl chloride. A few examples of nitrile reduction, which can also be carried out catalytically, are given below:



[559]

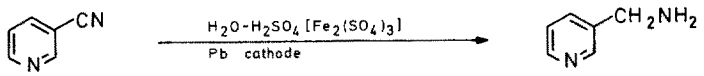


[560]



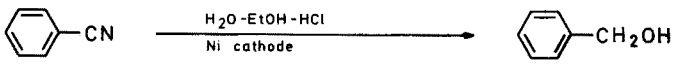
Yield: 95% [561]

On the other hand, for the reduction of heterocyclic nitriles, the electrochemical reduction can compete with catalytic methods. For example, Reilly [562] produces aminomethylpyridines by electrochemical reduction of the corresponding nitriles:

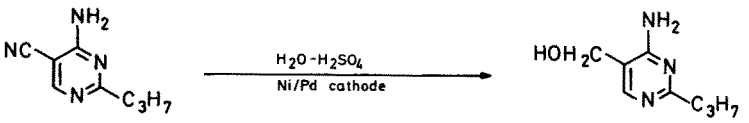


Yield: 55%

In aqueous acidic electrolytes, nitriles are also converted into alcohols:

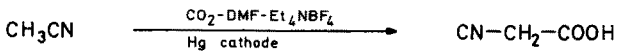


Yield: 95%
[563]



Yield: 75%
[564]

In extremely aprotic electrolytes, nitriles can be cathodically deprotonated and reacted with CO_2. However, the current efficiencies of these reactions are very low, so that they are only of scientific interest:



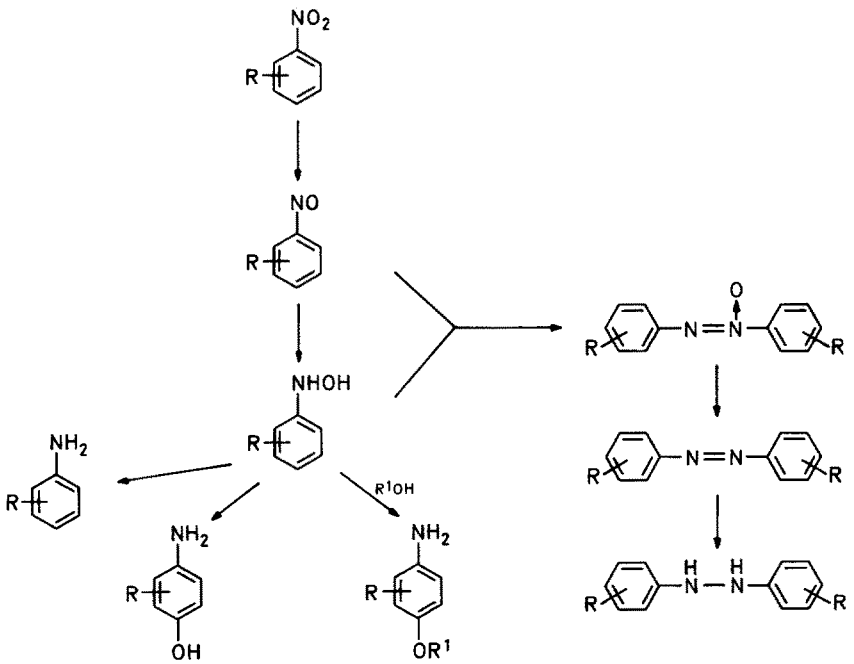
Current efficiency: 9%
[565]

3.2.4 Cathodic Reduction of Nitrogen Compounds

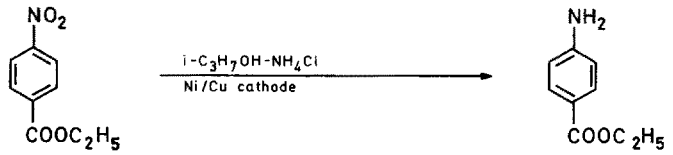
The cathodic reductions of nitro compounds are among the most thoroughly investigated reactions of organic electrochemistry. At least on the laboratory scale, the reaction permits the synthesis of many intermediates with different oxidation states. However, most syntheses can now also be carried out more economically by catalytic reactions. Therefore, only a few electrochemical reactions are still of industrial interest, i.e. the single-step syntheses of hydroxylamines, aminophenols, or anisidines.

3.2.4.1 Aromatic Nitro Compounds

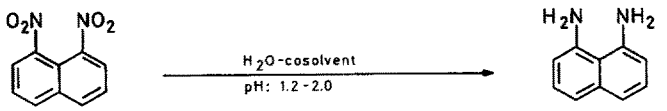
The various potential reactions are shown in a simplified form in the scheme below:



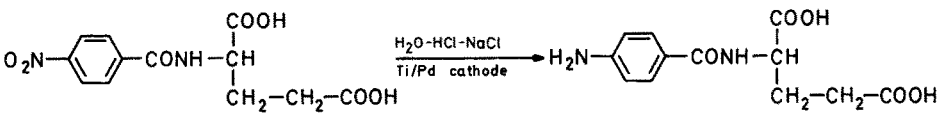
The reduction of the NO_2 group to the corresponding anilines is generally carried out in acidic to neutral electrolytes. Since the reaction can generally be carried out more economically by a catalytic method, there are only a few examples of this reduction in the recent patent literature [566–568]:



[566]
Intermediates for drugs



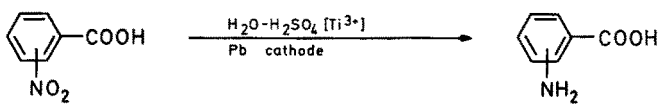
[567]
Intermediate for dyes



Yield: 99%
Current efficiency: 88% [568]
Intermediate for folic acid

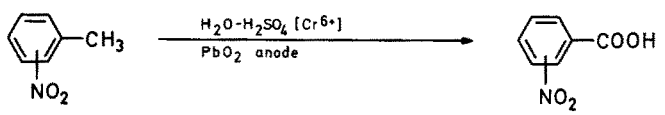
Since the synthesis has to be carried out in divided cells, an attempt was made also to use the anode compartment of the cell to obtain a useful product. An example of this is the synthesis of *p*-aminobenzoic acid from *p*-nitrotoluene [569]:

Cathode:



Selectivity: 82%

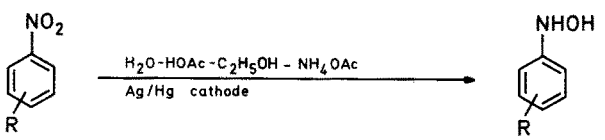
Anode:



Selectivity: 85%

The use of cells containing solid electrolytes for aniline syntheses was suggested by PPG [570].

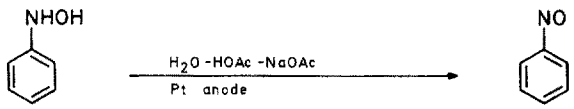
Of greater interest than the syntheses of anilines is the possibility of producing hydroxylamines from the corresponding nitro compounds.



R	Yield [%]
H	79
3,4-Cl	85
3-OH	90 (isolated as oxadiazolidinone)

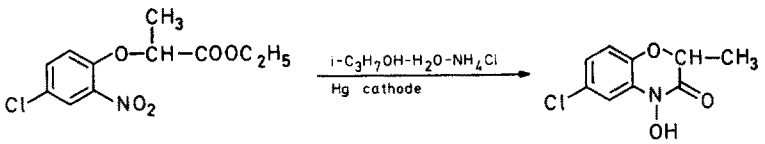
Intermediates for crop protection agents [571]

In the electrochemical reduction of the nitro compounds, the reaction passes smoothly through the intermediate stage of the nitroso compounds. However, the hydroxylamines can be converted anodically into the nitroso compounds [572]:



Current efficiency: 50%

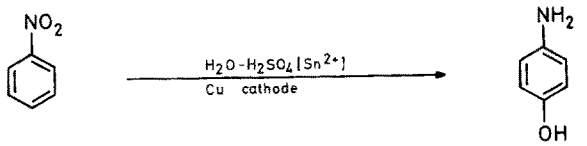
The electrosynthesis of hydroxylamines was also used for the production of cyclic hydroxamic acids [573] on the laboratory scale:



Yield: 92%
Current efficiency: 89%
Intermediate for crop protection agents

The most important reactions of this type are single-stage syntheses of aminophenols from nitroaromatics [574–578].

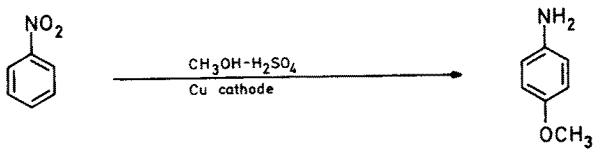
The best results were obtained at Cu cathodes in electrolytes containing sulfuric acid at elevated temperatures:



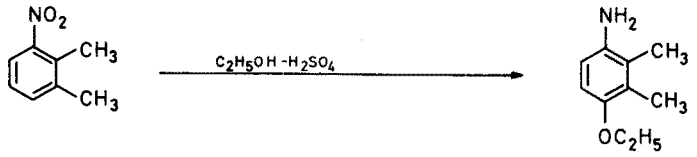
Yield: 90%

The use of a fixed-bed cell with Cu particles as the cathode [576] has been suggested for the synthesis. *p*-Aminophenol, produced by electrochemical reduction of nitrobenzene, was used for the synthesis of hydroquinone [577]. According to recent work, the addition of emulsifiers, for example, trialkylamine oxides [578], is supposed to suppress the formation of aniline as a byproduct. The electrosynthesis of *p*-aminophenol from nitrobenzene is carried out industrially in India [276].

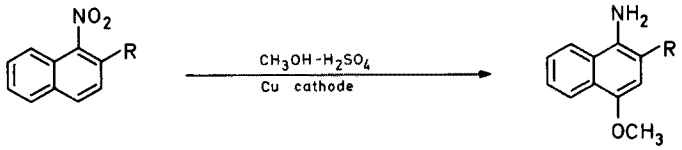
If the electrochemical reduction of nitrobenzenes is carried out in alkanols under comparable conditions, the corresponding alkoxy-substituted anilines are formed:



Conversion: 99%
Yield: 64%
Current efficiency: 57% [579-580]
Dye intermediate



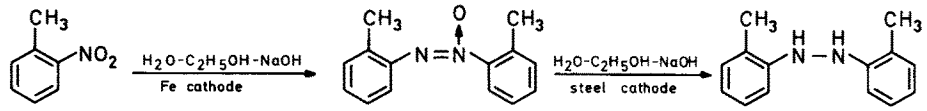
Yield: 76% [581]
Dye intermediate



[582]

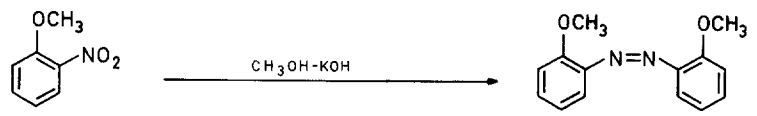
R	Yield
H	71%
CH_3	65%

In an alkaline electrolyte, nitroaromatics form the corresponding azoxy, azo, or hydrazo compounds, depending on the amount of current applied per mole of substrate.



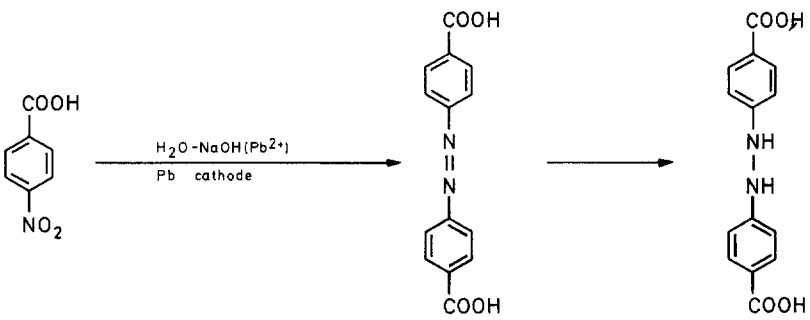
Yield: 99%
Current efficiency: 98%

Yield: quantitative
Current efficiency: 70%
[583]



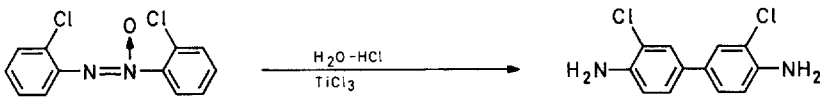
[584]
Dye intermediate

Dye intermediate
[585]



Yield: 97-99%
[585-589]
Dye intermediate

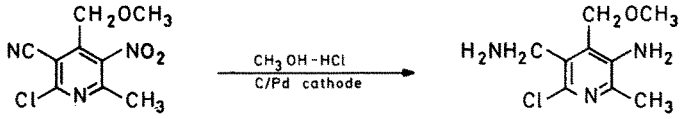
Hydrazobenzene is also to be produced in India [276] by electrochemical reduction of nitrobenzene. Azoxybenzenes can be reduced to benzidines with $TiCl_3$ in a solution containing hydrochloric acid [590]:



Yield: 80%
Dye intermediate

$TiCl_3$ can be electrochemically regenerated at graphite electrodes coated with titanium carbide [591].

Heteroaromatic nitro compounds are electrochemically reduced in a similar manner. An example of simultaneous reduction of the nitro and cyano function has been described by Tanabe [592]:

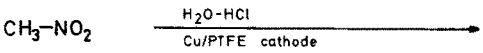


Yield: 97%

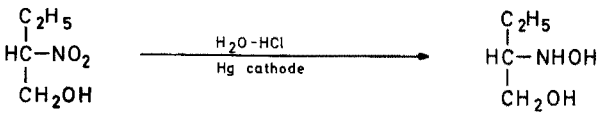
3.2.4.2 Aliphatic Nitro Compounds

Aliphatic nitro compounds can be reduced to hydroxylamines or amines, depending on the reduction conditions.

Examples of hydroxylamine syntheses are reductions of nitromethane [593] and 2-nitrobutan-1-ol [594]:

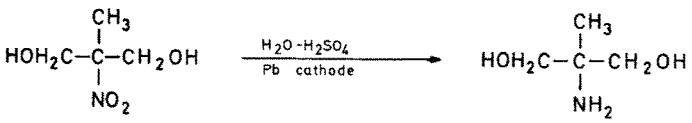


Yield: 98%
Current efficiency: 96%



Yield: 36%
Drug intermediate

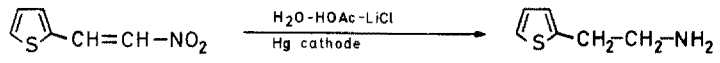
The reaction was used by Schering Corp. [595] for the synthesis of antibacterial hydroxylaminoeverninomicins. An example of the reduction of nitro compounds to the corresponding amino derivatives is the synthesis of aminoalcohols [596]:



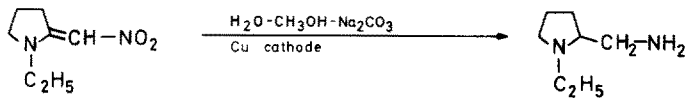
Yield: 95%
Current efficiency: 67%
Drug intermediates

3.2.4.3 Unsaturated Nitro Compounds

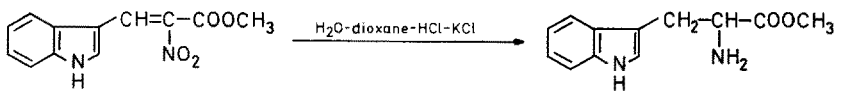
The reduction of α, β-unsaturated nitro compounds permits the introduction of aminomethyl groups, a reaction frequently used in the synthesis of drug intermediates:



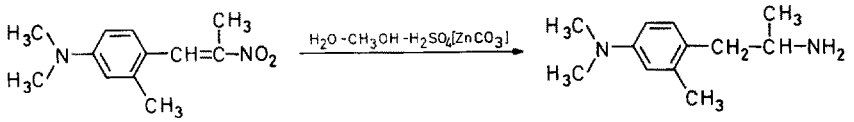
Yield: 47% [597]



Yield: 95% [598]



Yield: 62% [599]

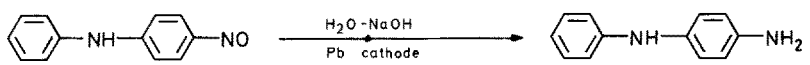


Yield: 86% [600]

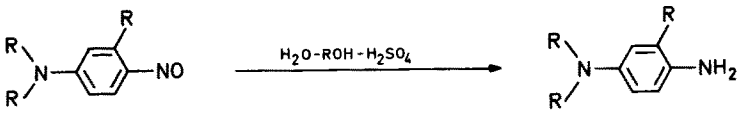
The addition of small amounts of hydroxylammonium salts increases the yields [600].

3.2.4.4 Nitroso Compounds

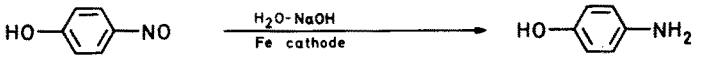
The reduction of nitroso compounds has been used for the synthesis of aminodiphenylamines [601-602], substituted *p*-phenylenediamines [603], and aminophenols [604] on the laboratory scale:



Yield: 96%
Dye intermediate

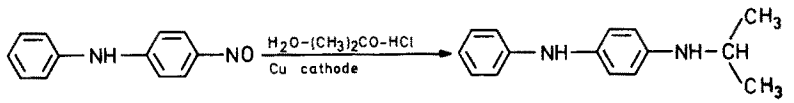


Yields not specified



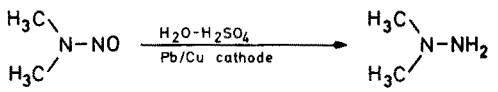
Yield: 95%
Current efficiency: 96%
Dye intermediate

The reduction of nitroso compounds in the presence of ketones can be used for the reductive alkylation of amines:

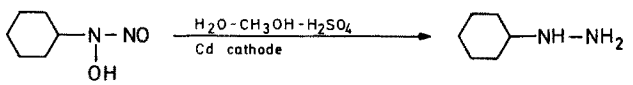


Yield: 98%
Current efficiency: 36%
[605]

N-nitroso compounds are reduced to hydrazines:

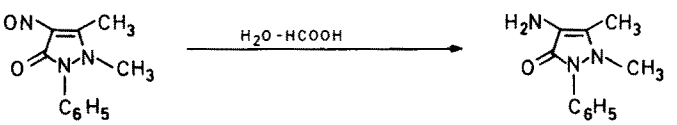


[606]



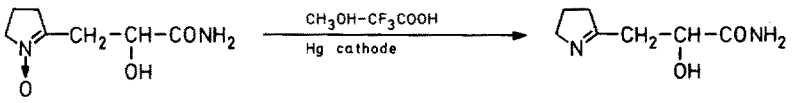
Yield: 55%
Current efficiency: 48%
[607]

The reduction of nitrosopyrazolones was used for the synthesis of aminopyrazolones [608]:



Yield: up to 90%

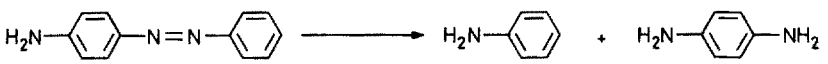
N-oxides can be converted electrochemically into the corresponding amines. One of the uses of the reaction is for the synthesis of bactericides.



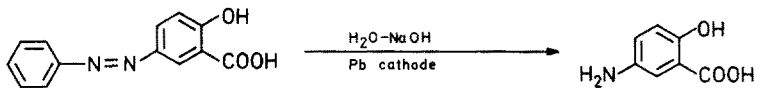
Yield: 57% [509]

3.2.4.5 Azo Compounds

The electrochemical reduction of azo compounds leads to amines, with cleavage of the N—N bond. The reaction can be used for introducing amino groups into aromatics:

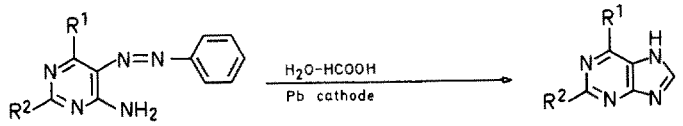


Yields not specified [610]

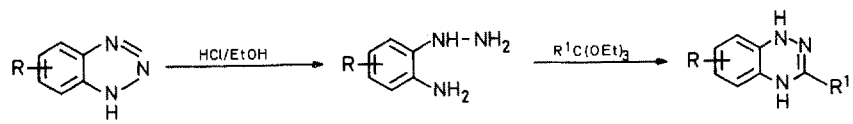


Yield: 86% [611]

The reaction was used for the synthesis of purines [612–615] and benzotriazines [616]:



R^1 = H, R^2 = NH_2:	Yield: 73%
R^1 = NH_2, R^2 = NH_2:	Yield: 80%
R^1 = NH_2, R^2 = OH:	Yield: 81%
R^1 = OH, R^2 = H:	Yield: 80%



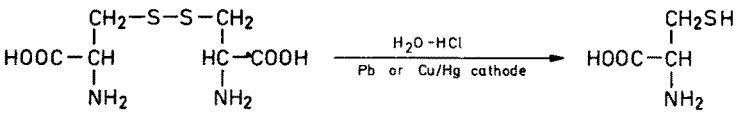
A new phenylhydrazine synthesis, investigated thoroughly by Hoechst [617–618], is of industrial interest:

Yield: 94%
Current efficiency: 94%

Aniline can be reused for the synthesis of the starting material diazoaminobenzene.

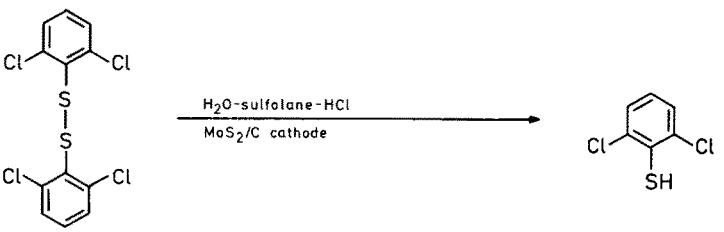
3.2.5 Cathodic Reduction of Sulfur Compounds

Disulfides are electrochemically reduced to mercaptans in virtually quantitative yields. An industrial example of this reaction is the reduction of cystine to cysteine by Diamalt [619] and, since 1985, also by Isochem [620]:



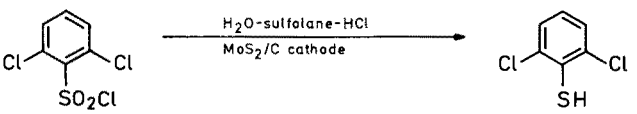
Yield: 99%
Current efficiency: 92%

Although the synthesis has long been known, the recent patent literature contains a number of Japanese applications [621-625] claiming special process variants. The reaction is also possible with aromatic disulfides [626]:



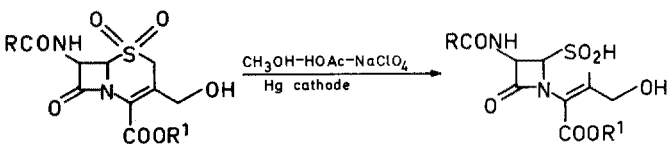
Yield: quantitative
Current efficiency: 30-60%
Polymerization modifier

The reduction of the corresponding benzene sulfonyl chlorides passes smoothly through the intermediate stage of the disulfides [626]:



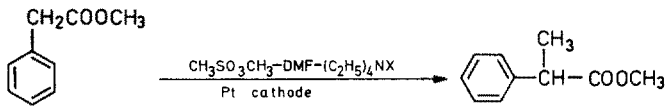
Yields not specified

The possibility of reducing sulfones to sulfinic acids was used for the synthesis of substituted 4-oxoazetidines [627-628]:



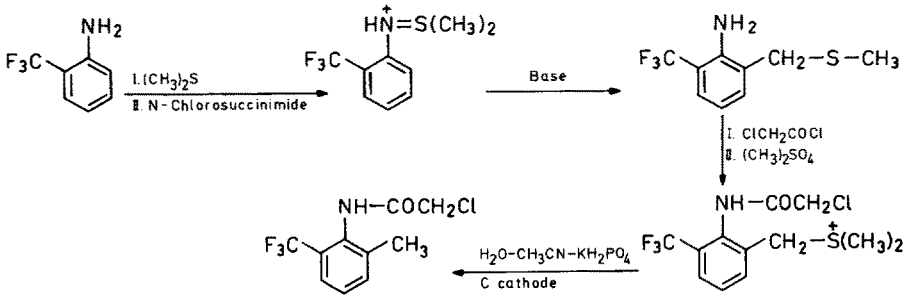
Yield: 52-70%

In analogy to the reduction of aliphatic halogen compounds, the reduction of sulfonates can be used for the alkylation of phenylacetic acids [435]:



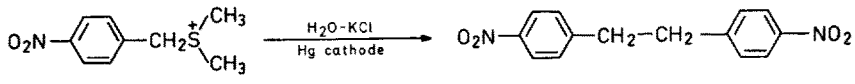
Yield: 78%

The reductive cleavage of sulfonium salts is a key step in the synthesis of new herbicides [629]:

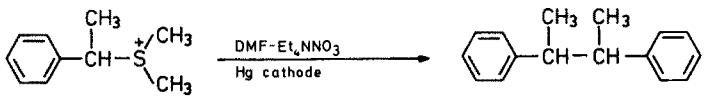


Yield: 94%
Current efficiency: 91%

Dimethyl sulfide can be recycled in this process. The reduction of sulfonium salts can also be used for C—C coupling:

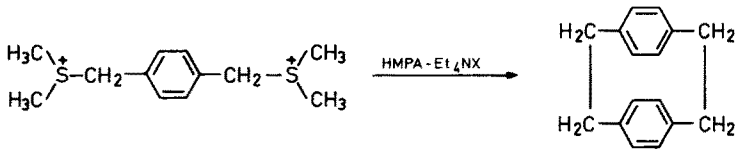


Yield: 95% [630]



Yield: 64% [631]

Paracyclophanes, however, are formed only in very low yields:



Yield: 8% [632]

4 Some Preconditions for the Realization of Electroorganic Syntheses in Industry

Because of the large number of patent applications and the comparatively small number of industrially implemented electroorganic processes, a number of university chemists may believe that electroorganic syntheses have hardly any prospects in industry. This conclusion, however, should not be drawn. If a comparison is made with the number of patent applications in other areas of organic chemistry, it will be found that organic electrochemistry is, if anything, still underrepresented. However, the number of companies filing patents in this area has increased again recently.

The question remains why so few electrochemical processes have been realized in industry to date. There appears to be no simple and general answer, since pure cost considerations (as, for example, in [633]) are responsible only for the choice of the process to be realized. Cost considerations alone are not the major basis for the decision whether the project should be realized at all in a company. The opinion that electroorganic syntheses have very high capital and energy costs and therefore cannot compete with conventional chemical processes is encountered very frequently.

This can be regarded as a prejudice. In processes with capacities up to 10,000 tonnes/year, the energy costs for electrolysis are frequently less than 15% of the production costs. The capital costs for the electrochemical part of the plant are in many cases only 30 to 40% of the overall investment. The electrolysis cells themselves generally account for less than 15%, and in the case of undivided cells frequently less than 5%. Thus, a simple work-up procedure for the discharged electrolysis solutions, including isolation of the end product and recycling of the electrolyte, is therefore decisive for the cost-effectiveness of an electroorganic process. Because of this problem not having been solved, a number of interesting laboratory syntheses have failed.

Over the past few years new electrosyntheses have been implemented industrially both in small companies (e.g., Otsuka, Isochem, Reilly Chemical) and in large companies (e.g., BASF, Hoechst). However, these involve fairly small capacities of 100

to 1000 tonnes/year for specialties. Since industrial cells (see Sect. 2) are now also available on the market, electrochemical processes can be implemented even by companies which do not wish to develop their own cell.

Although considerable progress has been made over the past 10–15 years, the range of highly selective electroorganic syntheses (where the catalytic method is inferior) has remained far too small for such syntheses to be used much more frequently in industry. As long as there is no decisive change in this respect, electroorganic chemistry will remain a technology which is used for specific isolated cases. It is also true that a „new technology" will only compete successfully if it has decisive advantages over established ones. Equality or marginal improvements are not in themselves sufficient to offset the risks involved in adopting a new method or replacing a proven process. This may be regrettable but, particularly in large companies, there is tough competition in the processing of attractive projects. Organic electrochemistry can only compete successfully here if it offers the substantially better solution to the problem.

During the course of scaling up electrochemical laboratory syntheses to the production scale, the following criteria have emerged as preconditions for the successful use of an electrosynthesis in industry:

- High product yields
- Current efficiencies: $> 50\%$
- Energy consumption (electrolysis): < 8 kWh/kg of end product
- Concentration of end product in the electrolyte: $> 10\%$
- Electrode lifetime: > 1000 h
- Membrane lifetime: (in divided cells) > 2000 h
- Simple isolation of the end product
- Simple removal and recycling of the electrolyte

Apart from the technical aspects, the general conditions for implementing an electrosynthesis are of critical importance. The prospects of the process increase when the project forms part of an important operation of the company or serves its strategic aims. The situation with intermediates, the company's own experience with electrosyntheses, and possible alternative processes will also influence the decision.

Experience over the past few years shows that, after a period of stagnation in the seventies, new electrosyntheses are once again being adopted by industry, even if the capacities are fairly small. Whether this trend continues will depend not at last on the development of the chemical industry. The environmental compatibility of electrochemical processes is certainly an asset of the method which will become even more important in the future.

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Organic Electroreductions at Very Negative Potentials

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Organic electroreductions at mercury cathodes in tetraalkylammonium (TAA^+) electrolyte solutions at the limit of the cathodic "potential window" are described. Aromatic hydrocarbons, fluorides, ethers and heterocycles, as well as aliphatic ketones, alkenes and alkynes have been studied, using both aqueous and non-aqueous solvents. At these very negative potentials neither the TAA^+ cation nor the mercury cathode are inert, instead they combine to form TAA-mercury. It is hypothesized, and supporting evidence is presented, that TAA-mercury serve as mediators in the organic electroreductions. The mediated reactions show remarkable selectivity in certain cases and it is shown that this selectivity can be improved by the choice of the TAA^+.

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1 Introduction

Electrochemical studies are usually performed with compounds which are reactive at potentials within the "potential window" of the chosen medium; i.e. a system is selected so that the compound can be reduced at potentials where the electrolyte, solvent and electrode are inert. The reactions described here are distinctive in that they occur at very negative potentials at the limit of the cathodic "potential window". We have focused here on preparative reductions at mercury cathodes in media containing tetraalkylammonium (TAA^+) electrolytes. Using these conditions the cathodic reduction of functional groups which are electroinactive within the accessible "potential window" has been achieved and several simple, but selective organic syntheses were performed. Quite a number of functional groups are reduced at this limit of the cathodic "potential window". They include a variety of benzenoid aromatic compounds, heteroaromatics, alkynes, 1,3-dienes, certain alkyl halides, and aliphatic ketones. It seems likely that the list will be increased to include examples of other aliphatic functional groups.

At very negative potentials neither the TAA^+ cation nor the electrode are inert, instead they combine to form reduced TAA-metals. Recent work has led us to formulate the hypothesis that TAA-metals are involved in many organic reductions done in the presence of TAA^+ salts at very negative potentials. These species are formed at the electrode surface and may act as mediators for electron-transfer to the organic substrates. A simplified mechanism for this catalytic sequence is shown below.

$$TAA^+ \xrightarrow[e^-]{M(cathode)} TAA\text{-metal}$$

$$Ox \xrightarrow{TAA\text{-metal}} Red$$

The formation of TAA-metals by cathodic reduction of TAA^+ cations at several solid electrodes has recently been reported [1]. These coloured materials were observed at Hg, Pb, Sn, Bi and Sb cathodes, while Pt and Cr were unreactive. They all act as reducing agents and seem to incorporate both TAA^+ and metal atoms (from the cathode) into their structure. They behave similarly and are probably related to the compounds resulting from the reduction of TAA^+ at graphite cathodes [2]. The best known and most extensively studied TAA-metals are those generated at mercury cathodes. They are also the likely catalysts for the organic electroreductions described below. Because TAA-mercury may be pervasively involved in the preparative reductions which are the topic of this review, the next few paragraphs provide information about their composition and evidence for their involvement as catalysts.

Numerous works [3] have been published describing the formation of black solids from the reduction of simple TAA^+ cations at mercury cathodes. It was realized that the black solids incorporate metal from the cathode and they became known as "TAA-amalgams". However, since recent publications dispute the similarity of these materials to what are classically regarded as amalgams, we prefer the term "TAA-mercury". The early information on TAA-mercury was qualitative in nature and most reports merely documented the observation of these materials. A more comprehensive study was that of Brauer and Dusing [4]. They observed $(CH_3)_4N$-mercury in acetonitrile and ethanol, $(C_2H_5)_4N$-mercury in acetonitrile and $(C_4H_9)_4N$-mercury in

DMF. They confirmed previous observations that $(CH_3)_4N$-mercury is relatively stable, that it is a solid with crystalline structure and its composition[1] is $(CH_3)_4N^+/Hg_{11\pm1}$. Similar results were obtained by Littlehailes and Woodhall [5]. Using coulometry, they determined $1e^-/(CH_3)_4N^+$ and from x-ray powder photographs, found evidence for crystallinity of the product. By means of colorimetry they evaluated the ratio $(CH_3)_4N^+/Hg$ as 1/12–13. In the same year Bratu and Balaban [6] reported a ratio of 1–7 for $(CH_3)_3NC_{16}H_{33}$-mercury. Littlehailes and Woodhall [5] studied the reduction of several TAA^+ cations in DMF and acetonitrile, using concentrations of 0.1–1.0 M and a cell voltage of 10–20 V. They observed that after the cell voltage was disconnected, a residual potential remained between the mercury cathode and a reference electrode. This was an indication that TAA-mercury formed in the reduction process maintained reducing power. Indeed, their experiments showed that isolated $(CH_3)_4N$-mercury reduced water, aqueous HCl, butyl iodide and acrylonitrile. An important finding was that the residual potential of a TAA-mercury depends on the cation. The values measured for $(CH_3)_4N^+$, $(C_2H_5)_5N^+$, $(C_3H_7)_4N^+$ and $(C_4H_9)_4N^+$ were —2.6, —2.8, —2.9 and —3.0 V(SCE). This is in accord with the more recent work on pyrrolidinium cations (which will be discussed later) which demonstrated that the potentials at which TAA-mercury are formed depend on the cation and become more negative with increasing size of the cation.

Recently a series of dialkylpyrrolidinium (Pyr^+) cations have been studied in our laboratory [7–9]. These cations are reduced at relatively positive potentials and could be investigated electrochemically as low concentration reactants in the presence of $(C_4H_9)_4N^+$ electrolytes. Using cyclic voltammetry, polarography and coulometry, it was shown that Pyr^+ react by a reversible $1e^-$ transfer. The products are insoluble solids which deposit on the cathode and incorporate Pyr^+ and mercury from the cathode. Both the cation and the metal can be regenerated by oxidation. Quantitative analysis of current-time transients, from potential step experiments, showed that the kinetics of the process involve nucleation and growth and resemble metal deposition.

The stoichiometric composition of Pyr-mercury was determined [8,9] by using thin mercury films, plated onto a platinum disk, as the cathodes. Under conditions where the amount of mercury constituting the cathode limited the amount of Pyr-mercury that could be formed, it was found that the composition is 1 TAA^+/5 Hg. Similarly, it was found that the product of $(CH_3)_4N^+$ consists of $(CH_3)_4N^+$/5 Hg. In a recent work Bard and co-workers [10] used exhaustive electrolysis of $(C_4H_9)_4N^+$ at mercury in acetonitrile and suggested the stoichiometry $(C_4H_9)_4N^+$/4 Hg.

The process for reduction of Pyr^+ and $(CH_3)_4N^+$ could thus be formulated in an oversimplified[2] way as:

$$R_4N^+[\text{solution}] + 1\,e^- + 5\,Hg[\text{cathode}] \rightarrow R_4N^+(Hg_5)^-[\text{solid}]$$

1 The authors noted that the composition was determined after removal of most of the excess of mercury.

2 Because of the high energy of σ^* of the quaternary nitrogen, it is hypothesized that the electron density concentrates on the metal moiety. However, these materials do not behave as simple salts. The formula shown is the simplest empirical one derived from the ratio of the components. The real structure may involve several units or may even be a solid macrostructure on the cathode surface.

Table 1. Reduction of dialkylpyrrolidinium cations [9]

R_1	R_2	Volume[a] [Å^3]	E_p[b] [V(SCE)]	$E^{o\prime}$ [V(SCE)]
CH_3	CH_3	93	−2.65	−2.57
CH_3	C_2H_5	106	−2.66	−2.63
C_2H_5	C_2H_5	120	−2.70	−2.68
CH_3	C_3H_7	120	−2.71	−2.67
C_2H_5	C_3H_7	134	−2.82[c]	−2.71

[a] Calculated using ChemGraph (E. K. Davis) distributed by Chemical Design Ltd., Oxford 1985; [b] 0.5 M solutions in DMF, $v = 50$ mV s^{-1}; [c] Only a small anodic peak was observed, even at high v

Although the spacial arrangement and the charge distribution in the product are yet unknown, a structure is envisaged which contains $(Hg_5)^-$ and Pyr^+ units. The cation remains relatively unperturbed by being desolvated and incorporated into the TAA-mercury film and its role is as a counter ion to (Hg_5) .

Comparing the reactivity of various Pyr^+ it was found that with increasing the size of the cation, the reduction potential becomes more negative and the Pyr-mercury product is less stable (Table 1). This could be due to coulombic and "packing" interactions within the solid. This hypothesis presents a rational explanation for the different behavior of the various Pyr^+ and for the enigmatic stability of Pyr-mercury as compared to other TAA-mercury. As an example dimethylpyrrolidinium exhibits a reversible cyclic voltammogram (CV) around −2.7 V(SCE) [7] at 20 mV s^{-1}. On the other hand, $(C_4H_9)_4N^+$ is only reduced ≈ -2.9 V(SCE) and an oxidation CV peak for $(C_4H_9)_4N^+$-mercury is observed ≈ -2.4 V(SCE) [11] at high scan rates ($v > 500$ mV s^{-1}). The chemical reactivity of Pyr^+ and $(C_4H_9)_4N^+$ should not be markedly different but according to the model, the different behavior is a result of cation size. The size of DMP^+ (93 Å^3) is comparable to that of $(Hg_5)^-$, while $(C_4H_9)_4N^+$ is much larger (231 Å^3) and destabilizes the ordered structure.

Several researchers that have been able to carry out preparative reduction of substrates, which in principle should be less reactive than the electrolyte, have been puzzled by the question, "How is electron-transfer to such substrates possible?". Some have proposed the intermediacy of TAA-mercury in the electron-transfer to the organic substrates. As examples, TAA-mercury were suggested [12] as possible mediators for the reduction of benzene at mercury cathodes with TAA^+ electrolytes and $(CH_3)_4N$-mercury was proposed [13, 14] as the electron transfer reagent for the reduction of alkynes. Conclusive evidence for the participation of $R_4N^+(Hg_5)^-$ in organic electroreductions, was obtained using dimethylpyrrolidinium (DMP^+) as the model. This cation was found to catalyze the reduction of a series of difficult to reduce [$E_{1/2} < -2.8$ V(SCE)] organic functional groups [15]. The catalytic sequence involves the initial formation of $DMP^+(Hg_5)^-$ at the cathode

$$DMP^+(Hg_5)^- + Org \rightarrow Org^{\cdot -} + DMP^+ + 5\,Hg$$

surface, followed by electron-transfer to the substrate. It was observed by CV and some of its kinetics were elucidated by analysis of polarographic measurements [16]. Preparative electrolyses [16–18] of organic substrates were carried out, in the presence of catalytic amounts of DMP^+, at the reduction potential of the catalyst. Although the substrates were electroinactive at these potentials in the absence of DMP^+, products were formed via the intermediacy of $DMP^+(Hg_5)^-$.

The catalytic effect of DMP^+ can be best demonstrated with an example. Consider the reduction of cyclohexanone [16]. This substrate does not exhibit a polarographic wave, nor a CV reduction peak (Fig. 1a and 2a). On the other hand, DMP^+ shows

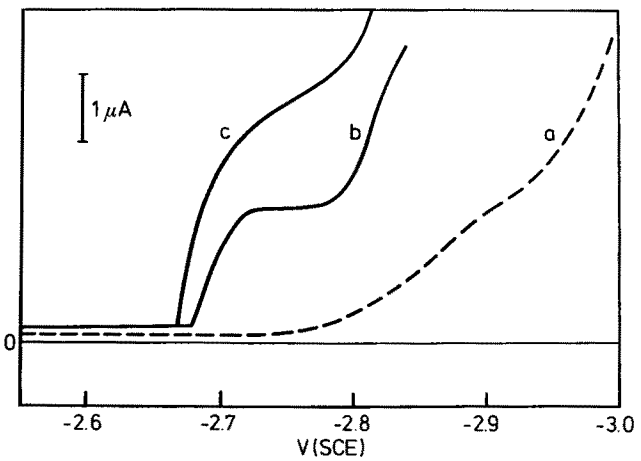


Fig. 1. Polarograms for the Catalytic Electroreduction of Cyclohexanone [16]: 0.1 M $(C_4H_9)_4NBF_4$ in DMF. a) 0.02 M Cyclohexanone; b) 0.002 M $(DMP)BF_4$; c) a + b

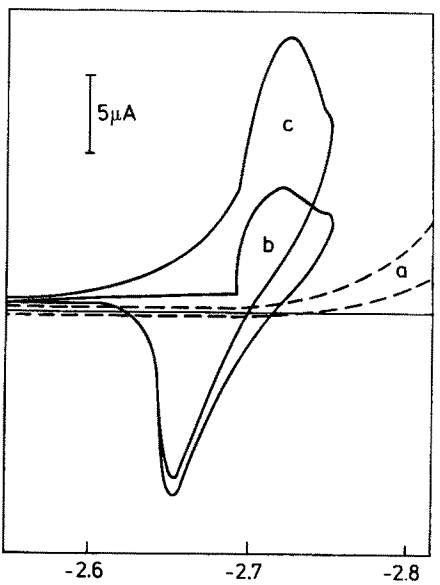
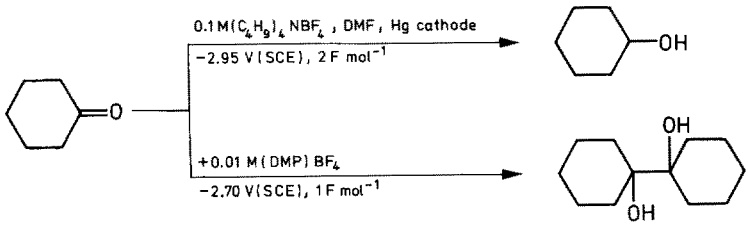


Fig. 2. Cyclic Voltammograms for the Catalytic Electroreduction of Cyclohexanone [16]: sessile hanging mercury drop electrode, 0.1 M $(C_4H_9)_4NBF_4$ in DMF. a) 0.02 M Cyclohexanone; b) 0.002 M $(DMP)BF_4$; c) a + b

a well-defined polarogram (Fig. 1b) and a CV (Fig. 2b) with shapes consistent with reversible formation of an insoluble solid. When both DMP^+ and cyclohexanone are present in the solution, an increase of the polarographic limiting current of DMP^+ is observed (Fig. 1c). Similarly in CV, an increase of the cathodic CV peak and a decrease of the anodic peak of DMP^+ are observed (Fig. 2c). These are clear indications for catalysis. The enhancement of the cathodic currents results from maintenance of the DMP^+ concentration near the cathode by the regeneration step.

Preparative electrolysis of cyclohexanone [17] in solutions containing 0.1 M $(C_4H_9)_4NBF_4$ as the electrolyte were carried out at −2.95 V(SCE), more positive potentials resulted in negligible current. When 0.01 M $(DMP)BF_4$ was added to the solution, electrolysis of cyclohexanone was possible at −2.70 V(SCE). Thus, DMP^+ caused a 0.25 V positive shift in the preparative reduction potential of cyclohexanone. DMP^+ also altered the nature of the product. In the presence of DMP^+, cyclohexanone formed only the corresponding pinacol, while in its absence cyclohexanol was the sole product. From this and experiments with other aliphatic ketones (that will be described later) it could be concluded that DMP^+ catalyzes the reduction and redirects the



the reduction pathway from 2 e^- to a 1 e^- reaction.[3]

This example and others in which DMP^+ was employed are particularly clear examples of catalysis. Similar mechanisms may be involved in less understood examples using more common electrolytes like $(C_4H_9)_4N^+$. An interesting example discussed below is the reduction of benzene to 1,4-dihydrobenzene, where evidence [15, 20] supports the involvement of $(C_4H_9)_4N$-mercury. In the case of benzene reduction, DMP^+ and other small, more easily reduced cations were ineffective compared to $(C_4H_9)_4N^+$. Different reactivity of various TAA-metals is now suggested for a few cases. One to be considered below is the reduction of 1,3-difluorobenzene [18]. Using $(C_4H_9)_4N^+$ a mixture of fluorobenzene and benzene was obtained. The use of DMP^+ allowed selective formation of fluorobenzene.

In summary, these studies of TAA-metals have suggested a useful mechanistic paradigm. This paradigm explains how products are formed when operating in the potential region where electrolyte should be decomposing; brings understanding to a number of otherwise unexpected observations reported below; and suggests methods for controlling the electrochemistry of the wide variety of compounds that reduce at very negative potentials.

3 TAA^+ have been reported to enhance dimerization within the "potential window". Specifically TAA^+ favor the formation of adiponitrile from acrylonitrile [5, 19]. However, since TAA^+ are inactive in this potential region their involvement may be different than described above.

2 Preparative Electrolysis Conditions

All cathodic reductions described below were performed at mercury pool cathodes in solutions containing tetraalkylammonium (TAA^+) electrolytes and most were carried out at a constant current. For preparative scale experiments, in general, the constant-current method is preferable to that of constant potential. The equipment for constant-current experiments is simpler, much less expensive and more suitable for large scale reactions. For the particular conditions described here, experiments at constant potential are difficult (except when TAA^+ in small concentrations are used as catalyst, see Sect. 8). The current often varies erratically throughout constant-potential experiments, reaction times are unpredictable and often impractically long. This is the result of participation of the cathode material in the reaction sequence. The mercury pool surface is visibly disrupted, droplets of mercury separate from the surface and in many instances the black precipitate of the TAA-mercury covers the cathode surface.

A variety of solvents have been used: acetonitrile and DMF which are common for organic electrochemistry, various aliphatic alcohols (methanol, ethanol, isopropanol, isobutanol and diethylene glycol), ethers (THF, diglyme, 1,2-dimethoxyethane, dioxane, trioxane) sulfolane and HMPA. Mixtures of organic solvents and water were also used. Most outstanding is the fact that some reductions could be carried out in water, without even a cosolvent. In all of these aqueous reactions (TAA)OH was the electrolyte and it was present in very high concentrations (10–55%). Most of the aqueous reductions required temperatures above ambient, probably to achieve some solubility of the substrates. Since the reduction of the organic reactants involves protonation steps it is not surprising that various proton donors were effective in facilitating reduction. Proton donors which were used as additives to enhance reduction rate (in addition to water) are methanol, ethanol, phenol and trifluoroacetic acid.

The most common electrolyte cations were tetrabutyl- and tetraethyl- but tributylethyl-, tributylmethyl- and tetra-n-propylammonium, and dimethylpyrrolidinium salts were also used. The common electrolyte anions were tetrafluoroborate, p-toluenesulfonate, perchlorate and acetate but, chlorides, bromides and iodides have also been used. The halides however, form halogens at the anode which tend to react with the organic substrate yielding unwanted byproducts [21]. Due to the availability of TAA^+ halides and their relatively low price attempts have been made to circumvent this complication. Cation exchange membranes [22, 23], as a cell divider, successfully inhibited diffusion of bromine into the catholyte. A different approach was to use $(C_4H_9)_4NBr$ in the catholyte only [24] and an aqueous acid solution as the anolyte in a divided cell. A creative solution to the "halide complication" which is relatively simple and may be applicable to other similar problems was to bubble ammonia over the anode [25, 26]. This method was so efficient in preventing oxidation of the bromide, that the organic substrate (naphthalene) could be reduced in an undivided cell.

Reductions were usually carried out in a divided cell. Ceramic thimbles, glass frits and cation exchange membranes have been used to separate the cathode and anode compartments. In some cases separation between the catholyte and the anolyte was not necessary. Reduction in undivided cells was particularly successful when aqueous

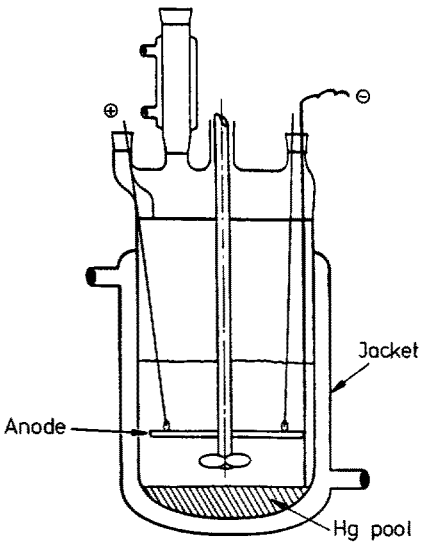


Fig. 3. Batch Reaction Cell [12]

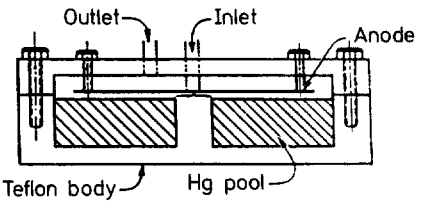


Fig. 4. Flow Cell [12]

(TAA)OH was used as the electrolyte solution. The inert atmosphere needed to avoid reduction of oxygen was usually achieved by bubbling nitrogen through the solution. The nitrogen stream served also for stirring, but in most experiments additional stirring devices (magnetic or mechanical) were also employed. Most reductions reported were batch experiments and several kinds of electrolysis cells were used.

Cells which are particularly convenient for work with mercury pool cathodes for both batch and continuous electrolysis were designed by Coleman and Wagenknecht [12] and shown in Fig. 3 and 4. In the batch cell (Fig. 3), the mercury placed at the bottom of a cylinder serves as the cathode and the anode is suspended above it in parallel. For experiments in a divided cell the anode is enclosed in a smaller cylinder (also suspended from the top) which serves as the anode compartment. In the continuous electrolysis cell (Fig. 4), the solution was circulated through the system by means of a pump. A repeat-cycle timer device was used to control the addition of reactant and the recovery of products. Anodes of various materials were used (Pt, graphite, platinized C, Ni, Sn, steel and DSA), but the nature of the anode did not seem to affect the reaction.

3 Benzene and Substituted Benzenes

The electron affinity of benzene is very low (−1.15 eV in the gas phase [27]) and its reduction requires strong reducing agents. The common method for reduction of benzenes, the Birch reduction, involves solvated electrons. These are generated by dissolving alkali or alkaline earth metals in liquid NH_3, low boiling amines or HMPA [28, 29]. The products are usually the corresponding 1,4-dihydrobenzenes which are obtained in high yield. Similar reductions have been carried out electrochemically [29–31]. In these cases, the organic substrates were reduced in the presence of Li^+ or Na^+ electrolytes. The common cathodes were platinum, graphite and vitreous carbon, and the solvents were liquid ammonia, methyl or ethylamine, ethylenediamine, HMPA and diglyme. Under these conditions the cathodic reaction generates solvated electrons which reduce the organic substrates.

Using aqueous $(C_4H_9)_4NOH$ or $(C_4H_9)_4NBF_4$ in THF-water, benzene could be reduced at mercury to 1,4-dihydrobenzene. During the reduction a black solid was observed. Under these conditions benzene shows no polarographic wave [31]. CV, however, gives some suggestion [11, 20] that $(C_4H_9)_4N$-mercury is a catalyst for this process. The electrolyte solutions without benzene give the voltammograms shown in Figs. 5a and 6a. They show the continuous rise in cathodic current expected for "background decomposition". On the return halfcycle there is a peak (at high sweep rate) suggested to be due to oxidation of $(C_4H_9)_4N^+$-mercury. Upon addition of benzene this anodic peak disappears (Figs. 5b, 6b) indicating that benzene reacts with the $(C_4H_9)_4N$-mercury. In agreement with this hypothesis are observations made by Coleman and Wagenknecht [12], who discovered that the current efficiency for benzene to 1,4-dihydrobenzene conversion using aqueous (TAA)OH was highest for the larger cations with more negative reduction potentials: $(C_4H_9)_4N^+$ — 100%; $(C_3H_7)_4N^+$ < 50%; $(C_4H_9)_3CH_3N^+$ — 30%; $(C_2H_5)_4N^+$ — trace; $(CH_3)_4N^+$ — trace.

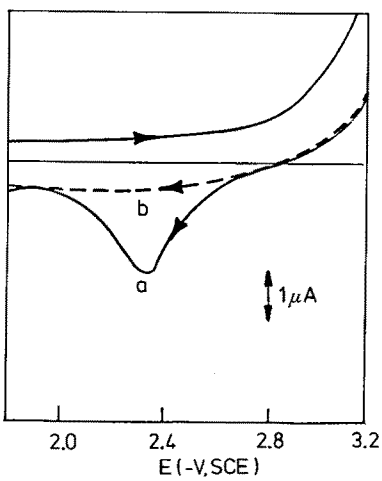


Fig. 5. Cyclic Voltammograms for the Catalytic Electroreduction of Benzene [11]: sessile hanging mercury drop electrode, reversal potential −3.2 V (SCE), $v = 10\,V\,s^{-1}$. a) 0.5 M $(C_4H_9)_4NBF_4$ in THF-2% H_2O; b) a + benzene (0.25 M)

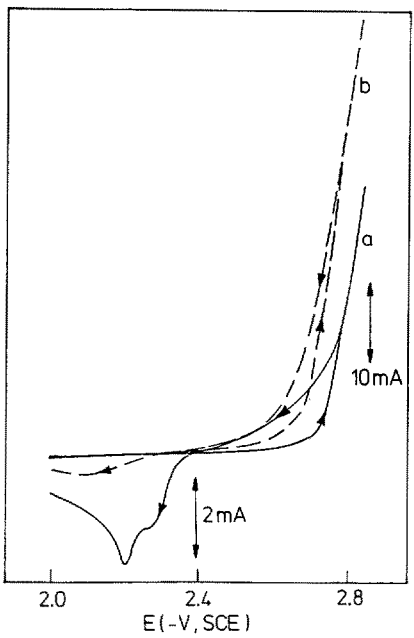


Fig. 6. Cyclic Voltammograms for the Catalytic Electroreduction of Benzene [20] (data collected digitally and plotted with a scale change at the end of the first half cycle): hanging mercury drop electrode, $v = 5\ V\ s^{-1}$. a) 1.0 M $(C_4H_9)_4NOH$ in H_2O; b) 5 ml (a) + 15 μL benzene

These data suggest that the reduction potential of benzene is quite negative so that a TAA^+ with a rather negative E° is required for reduction. In agreement with this idea the one-electron reduction potential of benzene has been estimated [32] to be −3.3 V(SCE) and recently $E_p = -3.42$ (SCE) has been proposed [33] from CV measurements (20 V s^{-1} at Pt in $(C_4H_9)_4NPF_6$, dimethoxyethane at −60 °C).[4]

Turning to preparative studies, a number of patents [23, 24, 34–41] have been registered for the cathodic conversion of benzene to 1,4-dihydrobenzene in solutions of $(C_4H_9)_4N^+$ electrolytes at mercury cathodes. The common electrolyte was $(C_4H_9)_4NBr$ in 1,2-dimethoxyethane [34], isobutanol [36], diethylene glycol [24, 37, 38], trioxane [23], various ethers [39], sulfolane [40] and ethylenediamine [41]. Often water was added to the solvent and in one case [35] an aqueous solution of $[(C_4H_9)_4N]_2SO_4$ and $(C_4H_9)_4NOH$ served as the electrolyte. Most patents reported constant-current electrolyses in divided cells and the current efficiencies of the process were 32–49%.

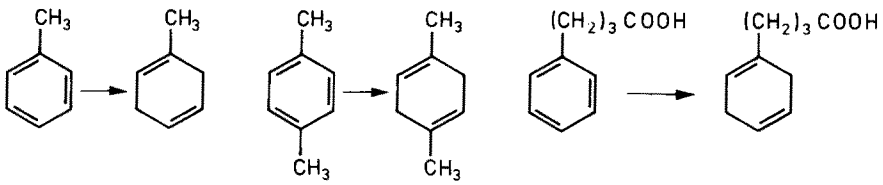
Electrolysis of benzene at a constant-potential of −3.3 V(SCE) in diglyme-H_2O (9–15%) with 0.4 M $(C_4H_9)_4NBr$ as the electrolyte [22] yielded 1,4-dihydrobenzene with 62% chemical yield and current-efficiency. In the Coleman and Wagenknecht [12] study on the cathodic reduction of benzene, they were able to obtain 1,4-dihydro-

4 Reversibility has not been demonstrated and the shape of the voltamogram seems to allow the possibility of a $(C_4H_9)_4N^+$ mediated process even at Pt.

benzene with high current efficiency (>90%) in both batch and continuous experiments. The outstanding features of this reaction, which make it synthetically and commercially attractive, are that it was carried out in an undivided cell with water as the only solvent. The optimum conditions involved 20–25% $(C_4H_9)_4NOH$ as the electrolyte at 60 °C and an O_2-evolving dimensionally stable anode. Steel or Ni anodes could also be used, but they corroded at pH lower than 13–14. Pt and carbon anodes were less adequate since they oxidized 1,4-dihydrobenzene back to benzene. Attempts to reduce benzene at several solid cathodes (glassy carbon, 75% Pb amalgam, 25% Cd amalgam, 3% Na amalgam, Wood's metal, Hg coated Cu, Cd, Pb and carbon) were unsuccessful. As indicated, the cation of the electrolyte had a pronounced effect on the current efficiency of the reaction.

Benzene was also reduced [11] at 0 °C in solutions of THF or diglyme containing 8% water and $(C_4H_9)_4NBF_4$ as the electrolyte. Reactions were performed at a constant current in a divided cell. The chemical yield of 1,4-dihydrobenzene was 70% and the current efficiency was higher than 90%. When DMF was used as the solvent, under similar conditions, the current efficiency of the process was low (25%), probably due to competing reactions of the solvent.

Toluene, like benzene, is polarographically inactive [31]; nevertheless, its cathodic reduction to 2,5-dihydrotoluene (*1*) is possible. Several patents have suggested use of $(C_4H_9)_4NBr$ in isobutanol [36], diethylene glycol [37] and sulfolane-water [40]. Using the same electrolyte in diglyme-water (9–15%) at a constant potential of −3.3 V(SCE),

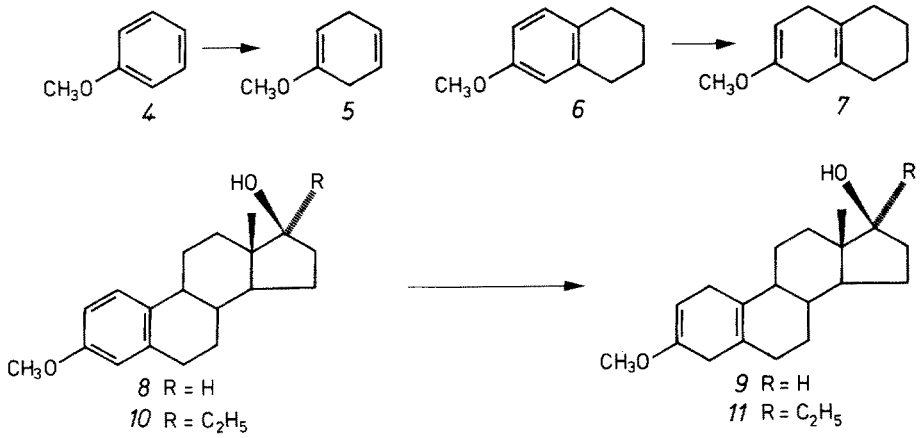


1 *2* *3*

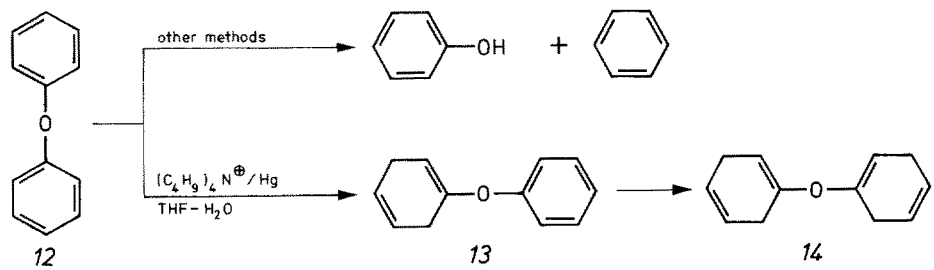
43% *1* was obtained after a charge equivalent to 1.6 F mol^{-1} was transferred (current efficiency of 54%) [22]. In 25% aqueous $(C_4H_9)_4NOH$ at 60 °C in an undivided cell toluene also formed *1* as the major product (74% of the crude electrolysis mixture) [12]. Under the same conditions [12] p-xylene and phenylbutyric acid yielded the corresponding 2,5-dihydro-derivatives *2* and *3*. However, *2* was formed in good yield (68% of electrolysis mixture) while the process for *3* was rather inefficient (30% current efficiency after 30% conversion).

Methoxybenzenes do not display CV reduction peaks, but they can be preparatively reduced in solutions of $(C_4H_9)_4N^+$ electrolytes. The reduction of *4*, *6*, *8* and *10* was achieved [11, 20, 42] in 40% aqueous $(C_4H_9)_4NOH$ at 60 °C in an undivided cell and in THF-8% H_2O with $(C_4H_9)_4NBF_4$ at ambient temperature in a divided cell. Under both sets of conditions the corresponding dihydroderivatives were obtained in high chemical yields (70–90%). However, the current efficiencies varied with the substrates and the electrolyte. In aqueous $(C_4H_9)_4NOH$ *5* and *7* were obtained with reasonable current efficiencies, 55% and 40% respectively. But, reduction of *8* and *10* was slow and the current efficiency was 18% for *9* and 6% for *11*. The difference in reactivity was due to the different solubility of the reactants in the medium and it could be improved by addition of THF to the electrolyte. In the mixed organic medium the

current efficiencies improved and the values for both *9* and *11* were 24%. In THF-8% H_2O all four substrates were soluble, reductions could be carried out at ambient temperature and proceeded with reasonable current efficiency (55–78%).



An example that demonstrates the possibilities inherent in the Hg cathode $-(C_4H_9)_4N^+$ electrolyte method, for the preparation of products which are inaccessible by other methods, is found in the reduction of diphenyl ether (*12*). The only products of *12* from reduction with alkali metals in liquid NH_3, amine solvent or HMPA [43b-e] were phenol and benzene, presumably arising from cleavage at the radical anion stage. Similarly phenol and benzene were formed by cathodic reduction



in dry DMF containing $(C_4H_9)_4N^+$ salts [44,45]. However, in aqueous solutions, hydrogenation of the benzene nuclei took place and formation of the previously unknown *13* and *14* competed with the reductive cleavage. In aqueous $(C_4H_9)_4NOH$ [43a], phenol and *14* were obtained in 36% and 44% yields, respectively, after transfer of 10 F mol^{-1}. Depending on the solvent, the amount of water, and the charge transferred, *13* could also be obtained in good yields (Table 2). Increasing the amount of water in DMF increased the yield of *13* up to 38% at 12% H_2O (at higher concentrations of water hydrogen evolution was significant). In this solvent *14* was formed only in small amounts. This is not surprising, since isolated benzenes are not efficiently reduced in DMF. In THF-8% H_2O, *13* was obtained (43% after transfer of 3 F mol^{-1}). But, in this solvent *13* could be reduced and upon additional charge transfer (5 F mol^{-1}) the tetrahydroderivative *14* was the major product.

Table 2. Reduction of diphenyl ether (*12*) [43,45]; 0.25 M $(C_4H_9)_4NBF_4$

Solvent	H_2O (%)	mA cm^{-2}	F mol^{-1}	Yield (%)	
				13	*14*
DMF	0	8	3	—	—
DMF	12	8	5	38	3
THF	8	8	3	43	6
THF	8	24	5	trace	52

These studies of reduction of benzenoid aromatics reveal that the solvent, the electrolyte cation, the current density and the water content are all important variables. In general it is important to have a rather negative potential (large TAA^+) and a proton source (water) present under conditions where hydrogen evolution or attack on the solvent does not occur. Under such conditions difunctional molecules can be selectively reduced by control over the number of Faradays/mole which are passed. This kind of predictable selectivity should give the electrochemical method real advantage over alkali metal reductions and the possibility to use materials other than liquid ammonia and alkali metal is quite attractive.

4 Alkynes and Alkenes

In the literature, much has been reported and tabulated concerning the electroreduction of alkynes and alkenes [46]. The bulk of this data involves activated substrates, compounds which are conjugated or substituted with electron withdrawing groups. The reduction of these compounds takes place at more positive potentials than isolated triple and double bonds due to the ability of the activating groups to stabilize the radical anion formed. The simple, isolated alkynes and alkenes, however, reduce beyond the "accessible" potential range of the common electrolyte-solvent systems. For example, in 1,2-dimethoxyethane [47] with $(C_4H_9)_4NClO_4$, 2,2',4,4',6,6'-hexa-t-butyldiphenylacetylene shows a wave with $E_{1/2} = -2.93$ V(SCE). In DMF with $(C_4H_9)_4NBr$ as the electrolyte, ethyne has an $E_{1/2} \simeq -3.0$ V where the electrolyte is already reduced while cyclononyne, 5-decyne, 1-hexyne, 3-hexyne and 2,2,5,5-tetramethylhexyne, show no waves [48].

The electrochemical generation of hydrogen in aqueous acid or alkaline solutions reduces unactivated alkynes [46a,b]. This process is similar to catalytic hydrogenation, however, and does not involve electron transfer to the substrate. The electrochemical generation of solvated electrons in amine solvents or HMPA has also been effective in reducing these compounds [29]. The focus of this section, however, is the electrolysis of these difficult to reduce alkynes and alkenes at mercury cathodes with tetraalkylammonium salts as electrolytes. Specific attention is also given to competitive reductions of benzenoid aromatics and alkynes or alkenes.

The preparative cathodic reduction of isolated triple and double bonds was investigated in solutions of $(CH_3)_4N^+$ and $(C_4H_9)_4N^+$ electrolytes. As indicated previously $(CH_3)_4N$-mercury is a weaker reducing agent than $(C_4H_9)_4N$-mercury.

$$CH_3CH_2CH_2CH_2C{\equiv}CH \rightarrow CH_3CH_2CH_2CH_2CH{=}CH_2$$

$$HOCH_2C{\equiv}CH \rightarrow HOCH_2CH{=}CH_2$$

$$HOCH_2C{\equiv}CCH_2OH \rightarrow \underset{HOCH_2}{\overset{H}{\diagdown}}C{=}C\underset{H}{\overset{CH_2OH}{\diagup}}$$

15 *16*

Indeed only alkynes could be reduced in $(CH_3)_4N^+$ solutions while alkenes were inactive. Reduction of 1-hexyne, propargyl alcohol and 1,4-butyne diol were performed [13] at a mercury cathode with $(CH_3)_4NCl$ as the electrolyte. The corresponding olefins were formed and the respective yields were 45%, 62% and 82%. The diacetate of *15* behaved similarly. However only the trans isomer *16* was formed from *15* while a mixture of trans and cis (6:4) isomers resulted from the reduction of the diacetate. Polarography of several alkynes in methanol with $(C_4H_9)_4N^+$ electrolytes showed [13] that they react close to background decomposition. It was therefore proposed [14] that $(CH_3)_4N^+$-mercury may be involved in the cathodic reduction of alkynes when $(CH_3)_4N^+$ salts serve as the electrolytes.

Attempts [13] to reduce several isolated alkenes in methanol with either $(CH_3)_4N^+$ or $(C_4H_9)_4N^+$ electrolytes were unsuccessful. Among others, 1-hexene, 4-phenyl-1-butene and allylbenzene were recovered intact after preparative electrolysis in this solvent.

Reduction of alkynes and alkenes in wet THF or diglyme with $(C_4H_9)_4N^+$ electrolytes seems to be more effective and several preparative experiments have been reported. Reduction of 1-hexyne at a constant current (16 mA cm^{-2}) in THF-H_2O (8%) with 0.25–0.5 M $(C_4H_9)_4NBF_4$ as the electrolyte led to the formation of 1-hexene in a good yield (65%) [11]. The reactant was completely consumed after transfer of 2.8 F mol^{-1} and the only byproduct formed was hexane (5%). Upon additional charge transfer the amount of hexane increased somewhat, but at a very small rate and after transfer of 4 F mol^{-1} its yield was only 10%. Thus it seems that cathodic reduction at these conditions is feasible for terminal alkynes, but very inefficient for the corresponding alkenes. Indeed attempts [49] to reduce 1-nonene under the same conditions as those employed for 1-hexyne were unsuccessful. After transfer of 4 F mol^{-1} less than 10% 1-nonane was obtained and most of the reactant was recovered.

Cathodic reduction of disubstituted alkynes is possible but proceeds with relatively low current efficiency. Reduction of 4-octyne under similar conditions as used for 1-hexyne yields only ≈50% 4-octene after transfer of 8 F mol^{-1}. It is interesting to note that the ratio trans/cis for the cathodically obtained 4-octene was ≈3/1. Other methods [29] involving electron-transfer reductions yield the corresponding trans isomers almost exclusively.

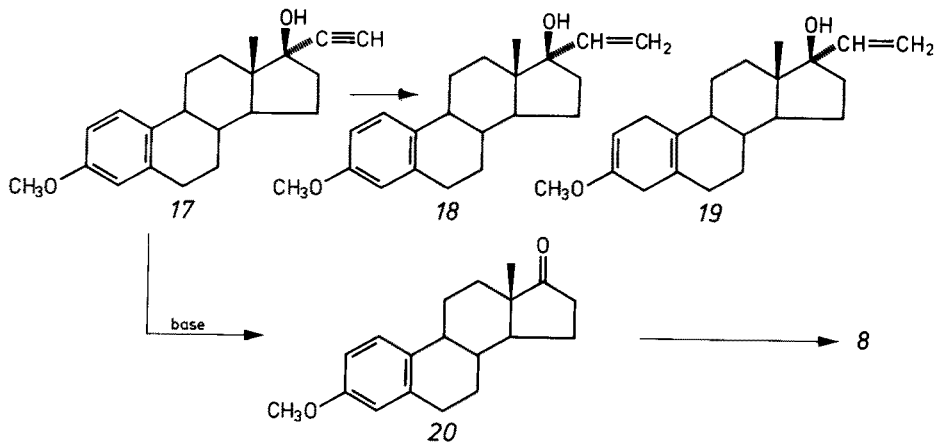
It has been of interest to know if the electrochemical method can provide functional group selectivity. As test cases the inter- and intramolecular competition between reduction of benzene rings and terminal alkynes were studied [45]. It was found that the amount of water in the solvent has a large effect on the ratio alkyne/benzene that reacted and that it could be used to control the ratio of alkene/dihydrobenzene prod-

Table 3. Reduction of an equimolar mixture of 1-hexyne/benzene [45]; 0.1 M $(C_4H_9)_4NBF_4$ in diglyme, I = 12.8 mA cm^{-2}, Q = 1 F mol^{-1}

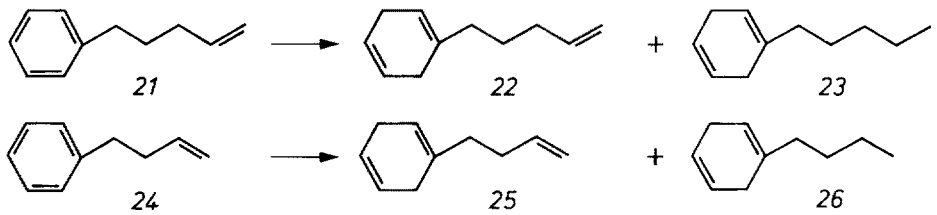
Yield (%)		
H_2O (%)	1-hexene	1,4-dihydrobenzene
1	26	10
4	26	33
8	14	41
12	8	38

ucts. The composition of the reduction product of an equimolar mixture of 1-hexyne/benzene in diglyme is shown in Table 3. Since this was an attempt to only determine the relative rates, reactions were not carried out to completion and the product was analyzed after ≈ 50% conversion (1 F mol^{-1}). It was shown that at 1% H_2O reduction of 1-hexyne predominates while at 8–12% H_2O 1,4-dihydrobenzene is the major product.

Cathodic reduction in THF-H_2O(1%) allowed the selective reduction [45] of the triple bond of *17* producing *18* in 68% isolated yield. As in the above, intermolecular competition at higher water concentrations, gave reduction of both functional groups. In the case of *17*, THF with more than 1% H_2O yielded mixtures of *18* and *19* [11]. This reaction also demonstrates the utility of the cathodic method for reduction of base sensitive substrates. Reduction of *17* using Li in liquid NH_3 yields *8* via *20* which results from base catalyzed elimination of the ethynyl [50]. It is noteworthy that cathodic reduction [42] of *17* in aqueous $(C_4H_9)_4NOH$ also yields *8*.

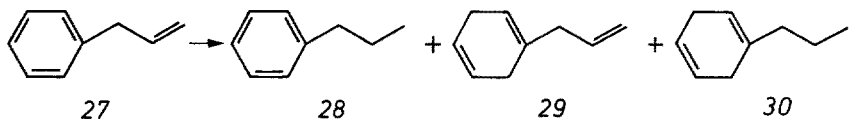


The inertness of olefins to cathodic reduction makes this method rather selective for reduction of benzene nuclei in molecules which also contain double bonds. Cath-



odic reduction[5] of *21* and *24* in THF-H_2O (4–12%) with 0.25 M $(C_4H_9)_4NBF_4$ gave the corresponding 1,4-dihydrobenzene derivatives *22* and *25* in good yield (60%) [45]. The reactants were completely consumed after transfer of 6 F mol^{-1} and the corresponding byproducts *23* and *26* were formed in relatively small amounts (15%). At lower water concentrations the composition of the cathodic products of *21* and *24* was similar, but the current efficiency of the reactions was lower.

The double bond of allylbenzene (*27*) is more reactive than the double bonds of *21* and *24* and competing reaction of the two functional groups is observed. The



competition depends on the water content (Table 4). The double bond reacted preferentially at low water concentration while the benzene ring was mainly reduced at the higher water concentrations. Thus depending on the amount of water *28* or *29* are obtained as major products. At medium water concentrations mixtures of *28*, *29* and *30* were formed. But these conditions were optimal if the reduction of both the benzene and the double bond functionalities was the target, and after transfer of 6 F mol^{-1} *30* was obtained in good yield. These results are quite similar to those

Table 4. Reduction of allylbenzene (*27*) [45]; 0.25 M $(C_4H_9)_4NBF_4$ in THF, I = 3.2 mA cm^{-2}

H_2O (%)	F mol^{-1}	Relative Yields (%)[a]			
		27	*28*	*29*	*30*
1	4	30	56	1	13
8–12	4	3	24	54	20
6	4	1	24	31	44
6	6	1	9	26	64

[a] The chemical yield of the crude product was ≈80%

5 The cathodic products from *21* and *24* in THF-H_2O (4–12%) are the same as those obtained with electrogenerated solvated electrons [51]. The latter method is more efficient in that it requires a charge of only 4 F mol^{-1}. It shows similar selectivity for the reduction of *21* but in the reduction of *24* the yield of the main product *25* is lower (52%) and that of the byproduct *26* is higher (34%).

reported [51] for the reduction of *27* with electrogenerated solvated electrons in methylamine with ethanol as the proton source.

From the limited data available, it seems that terminal alkynes can be efficiently reduced to the corresponding alkenes at mercury cathodes in $(C_4H_9)_4N^+$ electrolyte solutions. The cathodic reduction can be carried out in an organic-aqueous medium in which base related complications, associated with other electron-transfer reductions, can be avoided. Efficient reduction of alkenes has not proven possible. In competition, both benzenoid and alkyne functionalities are reduced. Selectivity can be improved by controlling the water content of the medium so that a terminal alkyne can be converted to an alkene in the presence of a benzenoid aromatic functionality.

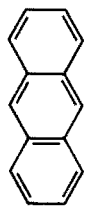
5 Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons contain extended conjugated π-electron systems and are electroactive within the cathodic "potential window" of many organic solvent/tetraalkylammonium electrolyte combinations. For many of them reduction potentials were measured and reported. It is important to note that the reduction of polycyclic aromatics involves consecutive electron-transfers and protonations. The nature of the product depends on the number of electrons and protons consumed and higher numbers result in more hydrogenated, less conjugated and thus less electroactive products. A simplified reduction scheme for polycyclic aromatics is shown below. The products are divided into three groups; (A) are reduced within the potential window and (B) require drastic reduction conditions as those described for the substrates in Chapt. 3.

polycyclic aromatic	⟶	conjugated π-systems (A)	⟶	isolated benzenes (B) ⟶ 1,4-dihydro benzenes (C)

Our focus here is on the formation of highly hydrogenated products. This process is of special interest for coal chemistry and the compounds which have been studied can be considered models for coal.

Anthracene (*31*) has been the subject of many electrochemical studies [52–54]. It exhibits [55] two polarographic waves at $E_{1/2} = -1.99$ and -2.71 V(SCE) in DMF -0.01 M phenol with 0.25 M $(C_4H_9)_4NBr$ as the supporting electrolyte. Preparative electrolysis [55] in this solution at -2.20 V(SCE) gave 90% 9,10-dihydroanthracene (*32*). More saturated products were obtained under conditions permitting reduction



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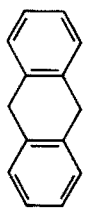

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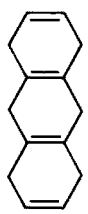

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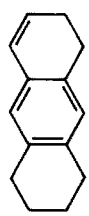

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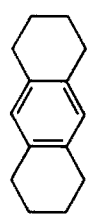

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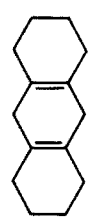

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Table 5. Reduction of anthracene (*31*) [56]; 55% aqueous $(C_4H_9)_4NOH$, 80 °C, I = 24 mA cm^{-2}

Cell	F mol^{-1}	Yield (%)				
		31	*32*	*33*	*35*	*36*
divided	6	41	29	20	5	4
divided	10 or more	15	3	75	4	2
undivided	10 or more	3	4	65	14	3

of isolated benzene nuclei (as described in Sect. 3). The products *32–36* were isolated and identified. Reduction [56] of anthracene in 55% aqueous $(C_4H_9)_4NOH$ at 80 °C, affected all three aromatic rings and after transfer of 10 F mol^{-1} the hexahydroanthracene (*33*) was obtained in good yield (Table 5). Lower concentrations of $(C_4H_9)_4NOH$ or temperatures were ineffective. Reduction of anthracene to *33* could also be achieved at ambient temperature or 0 °C in THF-H_2O (8%) with $(C_4H_9)_4NBF_4$. The yield of the major product *33* was 55%.

Using the optimum conditions for the reduction of anthracene to *33* (entry 2, Table 5) and adding a base catalyzed isomerization step for the conversion of *33* to *34* it was possible to increase the cathodic yields of the octahydro-(*35*) and decahydro-(*36*) products. The "one pot" sequence is shown below:

a) electrolysis at 80 °C (10 F mol^{-1})
b) reflux of mixture in the cell

31 ⟶ *33* + *34* + *35* + *36* + other
after the current disconnected (48 h) (34%) (9%) (26%) (21%) (6%)
c) electrolysis at 80 °C (10 Fmol^{-1})

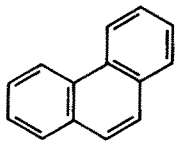
Phenanthrene (*37*) shows a polarographic wave [59] in dioxane-25% H_2O at $E_{1/2}$ = −2.4 V (SCE). It has been preparatively reduced [56] in $(C_4H_9)_4NOH$ under conditions similar to those employed for anthracene (Table 6). Depending on the amount of

Table 6. Reduction of phenanthrene (*37*) [56]; 55% aqueous $(C_4H_9)_4NOH$, 80 °C

mA cm^{-2}	F mol^{-1}	*37*	*38*	Yield (%)	
				Octahydro[a] phenanthrenes	Decahydro[c] phenanthrene
32	3	20	52	12	0
32	10	0	0	74[b]	17
8	20	0	0	27	54

[a] Mixture of three isomers; [b] The octahydrophenanthrene *39* constitutes 23% of this mixture; [c] One isomer in which the double bonds are nonconjugated

charge transferred, with a current density of 32 mA cm^{-2}, dihydrophenanthrene (*38*) or a mixture of octahydrophenanthrenes was the major product. At a lower current density (8 mA cm^{-2}), but with a longer reaction time decahydrophenanthrene was the major product and octahydrophenanthrenes were significant byproducts.



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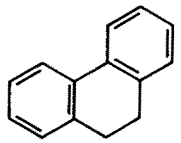

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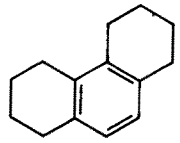

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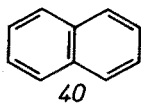
The cathodic reduction of naphthalene (*40*) has been the topic of numerous studies [58–60]. However, most were concerned with the mechanism of the initial electron-proton transfers. For example, in 0.5 M $(C_4H_9)_4NBF_4$ in DMF — 1.8% H_2O naphthalene exhibited [61] one polarographic wave, $E_{1/2} = -2.56$ V(SCE).

Several patents describe the preparative cathodic reduction of naphthalene to 1,4-dihydronaphthalene (*41*) using $(C_4H_9)_4NBr$ as the electrolyte in 2-methyl-1-propanol [36], diethyleneglycol [37] and sulfolane-water [40] as solvents. Connolly et al. [25, 26], obtained 93% *41* using 8% $(C_4H_9)_4NBr$ in diglyme-7% H_2O or THF-CH_3CN (1 : 1) containing 1% NH_3. The current density was 37–1080 mA cm^{-2} and the current efficiency was quantititative. Unique features of the last two patents [25, 26] are that they utilized an undivided cell and oxidation of NH_3 which was bubbled at the platinized C anode provided the counter reaction.



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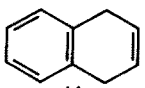

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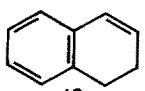

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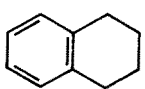

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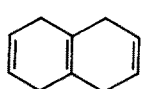

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The reduction of naphthalene was also performed in acetonitrile-water with $(C_2H_5)_4N^+$ tosylate as the electrolyte [62, 63]. Osa and co-workers [62] investigated the product composition of constant potential [—2.3 to —2.4 V(SCE)] electrolyses. Mixtures were analyzed after partial conversion (< 34%) of the reactant and the products were 1,4-dihydronaphthalene (*41*), tetralin (*43*) and trace amounts of 1,2-dihydronaphthalene (*42*). The effect of various reaction parameters on the product composition was tested. The effect of the electrolyte concentration in the range of 0.1–1.0 M was studied in solutions of CH_3CN-25% H_2O. Under these conditions the 1,4-dihydroderivative (*41*) was formed almost quantitatively, traces of tetralin (*43*) were present but no *42* was detected. The current efficiency for *41* increased with increasing the electrolyte concentration up to 0.33 M. It slowly decreased at higher electrolyte concentrations. Experiments with various amounts of water (0–30%) in the solvent, for 1.0 M $(C_2H_5)_4NOTs$ solutions, showed that in dry solvent tetralin (*43*) was the major product (30% current efficiency) together with small amounts of *41* and *42*. Addition of water altered[6] the composition of the product and 1,4-dihydronaphthalene (*41*)

6 A possible explanation for the change in product could be that in dry solvent protonation is slow and the more stable dihydroderivative *42* is formed. This product is electroactive and is further reduced to *43*. In the presence of water, protonation is fast and takes place at the sites of highest charge density yielding *41*. This product is electroinactive at these conditions and therefore constitutes the major component of electrolysis.

became the major product while *42* and *43* were present in trace amounts. At 5% water the current efficiencies were 50% for *41* and 5% for each *42* and *43*. Increasing the water concentration caused an increase in the current efficiency for the formation of *41* and at 25% water it was 75%. Above 25% water the current efficiency dropped, probably due to hydrogen evolution competing with the organic reaction.

Reduction of naphthalene under conditions suitable for reduction of isolated benzene rings resulted, as expected, in the formation of some 1,4,5,9-tetrahydronaphthalene (*44*). It was carried out [12] in 15% aqueous $(C_4H_9)_4NOH$ at 80 °C and the yield of the products and the low current efficiency (17% naphthalene remained unreacted in spite of the transfer of large excess charge) were caused by anodic side reactions, as the experiment was conducted in an undivided cell.

These studies of naphthalene, phenanthrene and anthracene reduction in aqueous $(C_4H_9)_4NOH$ or mixed solvents containing $(C_4H_9)_4N^+$ show that the aromatic hydrocarbons can be converted to rather highly saturated products. In general, although mixtures will always result, it should be possible to drive the process to get isolable quantities of products like hexahydroanthracene (*33*), octahydrophenanthrene (*39*) and tetrahydronaphthalene (*44*). The aqueous $(C_4H_9)_4NOH$ system is of considerable interest for large scale work in that it requires no organic cosolvent and it is highly conductive.

6 Bicyclic Heteroaromatics

Polycyclic aromatics with more than two aromatic rings, or more than one heteroatom are relatively easy to reduce and several reviews [64] have summarized works on their electrochemical behavior. Bicyclic heteroaromatics with one heteroatom are reduced close to or beyond the decomposition of the electrolyte unless acidic solutions are used. Very few compounds of this kind have been preparatively reduced in neutral media. Their cathodic reduction could be carried out at mercury cathodes with TAA^+ electrolytes. Depending on the heteroatom and the amount of charge transferred, hydrogenated and/or reductive cleavage products were obtained.

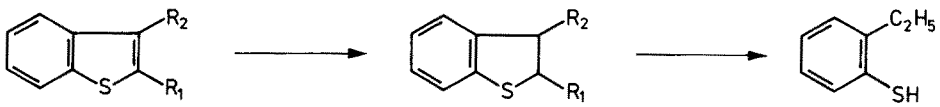
Polarographic measurements [65] of benzo[b]thiophene (*45*) and its 3-methyl (*48*) and 2-ethyl (*50*) derivatives in DMF containing $(C_4H_9)_4NI$ showed polarographic waves very close to background decomposition. Addition of water to the solvent caused a cathodic shift of the waves and $E_{1/2}$ for *45*, *48*, and *50* measured in DMF-1.1% H_2O were −2.655, −2.663 and −2.800 V(SCE) respectively. Preparative

Table 7. Reduction of benzo[b]thiophene (*45*) [43]; I = 24 mA cm^{-2}

Electrolyte	F mol^{-1}	Yield (%)		
		45	*46*	*47*
Aqueous 55% $(C_4H_9)_4NOH$, 80 °C	2	7	68	15
	6	8	6	77
0.1 M $(C_4H_9)_4NBF_4$, THF-8% H_2O, 0 °C	2	4	75	12
	4	8	0	54

electrolyses [65] of *45*, *48*, and *50* at a constant potential, at the foot of the wave [−2.60 to −2.62 V(SCE)], with either $(C_4H_9)_4N^+$ or $(C_2H_5)_4N^+$ electrolytes yielded the corresponding 2,3-dihydroderivatives *46*, *49* and *51*.

Reduction of benzo[b]thiophene (*45*) was also carried out [43] in aqueous 55% $(C_4H_9)_4NOH$ and 0.1 M $(C_4H_9)_4NBF_4$ in THF-8% H_2O. The products were *46* and 2-ethylbenzenethiol (*47*). Some results are shown in Table 7. The major product of *45* in either solvent was *46* after transfer of charge equivalent to 2 F mol^{-1} and *47* after transfer of 4 F mol^{-1} (or more). The chemical yield of *46* was somewhat better in the aqueous medium, while that of *47* was better in THF-H_2O. It was shown that *47* is the product of reductive cleavage of *46*. Electrolysis of *46* (2 F mol^{-1}) under conditions identical to those used for *45* gave 65% *47*. Thus *45* is first hydrogenated to *46* which is consequently cleaved (upon additional charge transfer) to *47*. It is interesting to note that *47* is the only reduction product of *45* formed by alkali metal in liquid NH_3 or amine solvent [66]. Obviously solvated electrons are more powerful and less selective reducing agents than $(C_4H_9)_4N$-mercury.

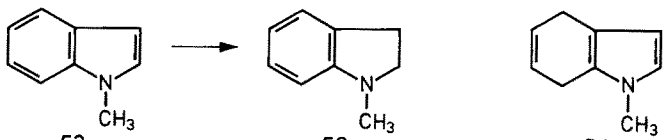


45 $R_1=R_2=H$
48 $R_1=H$, $R_2=CH_3$
50 $R_1=C_2H_5$, $R_2=H$

46 $R_1=R_2=H$
49 $R_1=H$, $R_2=CH_3$
51 $R_1=C_2H_5$, $R_2=H$

47

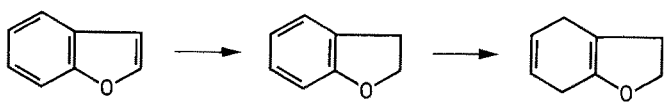
1-Methyl indole (*52*) does not show any reduction peak in cyclic voltammetry in diglyme-H_2O solutions with $(C_4H_9)_4NBF_4$ as the supporting electrolyte.



52 *53* *54*

Nevertheless it was preparatively reduced [67] in THF-H_2O (2–12%) with 0.35–0.5 M $(C_4H_9)_4NBF_4$. At a constant current (24 mA cm^{-2}) the reactant *52* was completely consumed after transfer of charge equivalent to 2 F mol^{-1} and the products were *53* (60%) and *54* (10%). It is noteworthy that reduction of *52* with Li in liquid NH_3 with ethanol also leads to dihydroderivatives [68] but it is less regioselective and the product composition is 32% *53* and 37% *54*.

Benzofuran (*55*) like *52* does not show reduction peaks in cyclic voltammetry (diglyme-H_2O, $(C_4H_9)_4NBF_4$). It could still be reduced efficiently in THF-H_2O with 0.25 M $(C_4H_9)_4NBF_4$. Reduction [67] in THF-H_2O (2–4%) was most efficient yielding over 80% 2,3-dihydrobenzofuran (*56*) and only traces (<7%) of the 4,7-dihydroiso-



55 *56* *57*

mer. Again the cathodic reduction was much more regioselective than Li-liquid ammonia with methanol which forms an equimolar mixture of *56* and 4,7-dihydrobenzofuran.

Cathodic reduction [67] of 2,3-dihydrobenzofuran (*56*) was also achieved. The optimum conditions were 0.25 M $(C_4H_9)_4NBF_4$ in THF-4% H_2O and a constant low current (4 mA cm^{-2}). The reactant was consumed after transfer of charge equivalent to 3 F mol^{-1} and the product was the tetrahydrobenzofuran (*57*) in 59% yield. Tetrahydrobenzofuran (*57*) could also be obtained directly by cathodic reduction of benzofuran (*55*) when charge in excess of 2 F mol^{-1} was transferred.

Thus, all three heteroaromatics, benzofuran, 1-methyl indole and benzo[b]thiophene were reduced at negative potentials to give reasonable yields of products. The regioselectivity was better than that observed for alkali metal/NH_3 reactions.

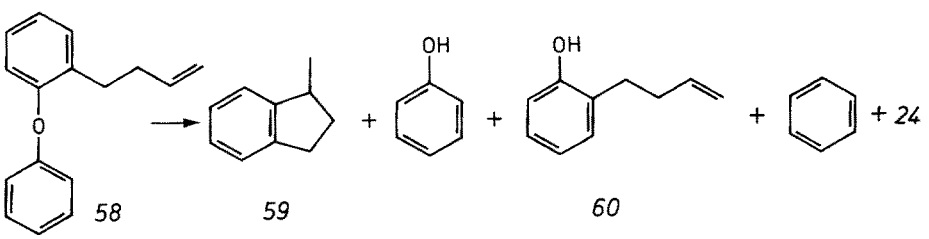
7 Reductive Cleavage

Cleavage is a common reaction pathway for substrates which, upon reduction to the intermediate radical-anion stage, may split off relatively stable anions. Often such substrates contain heteroatoms which stabilize the negative charge on the cleaved anion.

$$RY \rightarrow [RY]^{\cdot -} \rightarrow \begin{matrix} Y^- \text{ ----} \rightarrow \text{products} \\ + \\ R^{\cdot} \text{ ----} \rightarrow \text{products} \end{matrix}$$

Cathodic reductive cleavages have been reviewed [69] and most of the reported reactants were electroactive within the "potential window". However, some reductive cleavages took place at very negative potentials, where the TAA^+ electrolyte is decomposed and it is feasible that TAA-mercury were involved. The reductive cleavage of bicyclic heteroaromatics was presented in Sect. 6. Other cleavages at potentials < -2.8 V (SCE) are discussed in this section.

Diphenyl ether (*12*) shows a poorly resolved wave at a Pt cathode at $E = -2.95$ V (SCE) [44]. It was preparatively cleaved to phenol and benzene at mercury cathodes in dry DMF containing $(C_4H_9)_4N^+$ salts [44,45]. The cleavage proceeded with good chemical yield and current efficiency. An interesting intramolecular reductive cyclization was observed when o-(3-butenyl)phenoxybenzene (*58*) served as the substrate [44]. Electrolysis at -2.95 V(SCE) in DMF containing 0.2 M $(C_4H_9)_4NClO_4$ yielded significant amount of the cyclic hydrocarbon *59*. After transfer of 3–4 F mol^{-1} only trace amount of the reactant *58* remained and the product composition was *59* (47%), phenol (49%), *60* (47%), benzene 35% and *24* (5%).



58 *59* *60*

Loss of the cyano group was observed [70] during the cathodic reduction of ethyl cyanoacetate (0.1 M $(C_4H_9)_4NI$ in DMF). This substrate shows a wave with $E_{1/2}$ = −2.97 V(SCE). The only reduction product from preparative experiments was ethyl acetate in 75% yield.

$$N{\equiv}CCH_2COOC_2H_5 \rightarrow CH_3COOC_2H_5$$

Reduction of a series of difficult to reduce[7] benzyl alcohols [55] and ethers [71] in DMF with $(C_4H_9)_4N^+$ electrolyte showed that the hydroxyl and the ether functionalities can be cathodically removed with good selectivity. Examples are shown in Tables 8 and 9.

Table 8. Cathodic cleavage of benzyl alcohols [55]; 0.1–0.25 M $(C_4H_9)_4NI$ in DMF

Substrate	E[V(SCE)]	F mol^{-1}	Product	Yield
$(C_6H_5)_3COH$	−2.90	1.95	$(C_6H_5)_3CH$	95%
$(C_6H_5)_2CHOH$	−2.90	2.4	$(C_6H_5)_2CH_2$	80%
$C_6H_5C(OH)(CH)-C{\equiv}CH$[a]	−2.88	5.2	$C_6H_5CH(CH_3)CH_2CH_3$	90%
$(C_6H_5)_2C(OH)-CH{=}CH_2$	−2.80	3.5	$(C_6H_5)_2CHCH_2CH_3$	90%

[a] Phenol was added as proton source

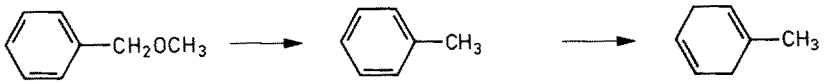
Table 9. Cathodic cleavage of benzyl ethers [71]; 0.15 M $(C_4H_9)_4NBr$ or 0.1 M $(C_4H_9)_4NI$ in DMF, Q = 2–2.2 F mol^{-1}

Substrate	E[a] [V(Ag/AgI/I$^-$)]	Products (yield)
$(C_6H_5)_3COCH_3$	−2.30	$(C_6H_5)_3CH$ (100%)
$(C_6H_5)_3COCH_3$[b]	−2.30	$(C_6H_5)_3CH$ (100%)
$(C_6H_5)_2CHOCH_3$	−2.40	$(C_6H_5)_2CH_2$ (70%) + $(C_6H_5)_2CHOH$ (30%)
$(C_6H_5)_2CHOCH_3$[b]	−2.40	$(C_6H_5)_2CH_2$ (90%)
$(C_6H_5)_2CHOCH(C_6H_5)_2$	−2.40	$(C_6H_5)_2CHOH$ (50%) + $(C_6H_5)_2CH_2$ (50%)
$C_6H_5CH_2OCH_2C_6H_5$	−2.40	$C_6H_5CH_2OH$ (50%)
p−$CH_3O(C_6H_4)CH(OCH_3)C_6H_5$	−2.45	p-$CH_3O(C_6H_4)CH_2C_6H_5$ (70%) + p-$CH_3O(C_6H_4)CH_2OH$ (30%)
p−$CH_3O(C_6H_4)CH(OCH_3)C_6H_5$[b]	−2.45	p-$CH_3O(C_6H_4)CH_2C_6H_5$ (100%)

[a] The potential of this reference electrode is 0.5 V negative of SCE [72]; [b] Phenol was added as a proton source

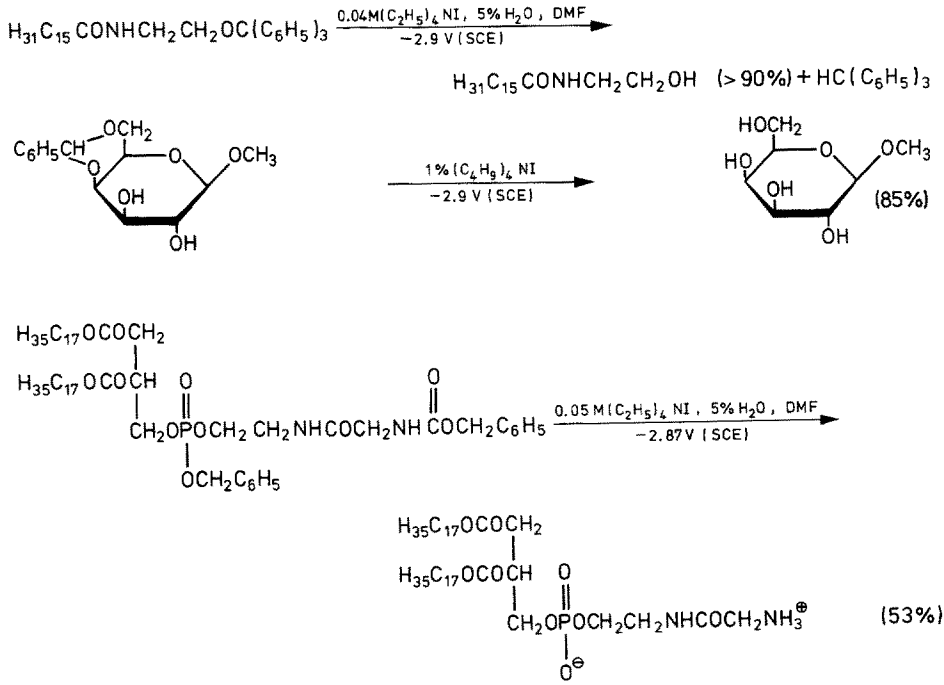
7 The authors [55] commented that these transformations may involve solvated electrons or TAA-mercury.

Benzyl derivatives of aliphatic alcohols [73] are not reduced below the discharge potential of $(C_2H_5)_4N^+$ in DMF [—2.9 V(SCE)]. But, they show a wave around —3.1 V(SCE) in solutions of $(C_4H_9)_4N^+$. Efficient reductive cleavage of benzyl methyl ether was achieved [11] in THF-8% H_2O with 0.25 M $(C_4H_9)_4NBF_4$. Under these conditions, toluene, which is the cleavage product may also be reduced and the



product depended on the amount of charge transferred. The chemical yield of the isolated product was 70% and it contained 92% toluene after transfer of 2 F mol^{-1} and 93% 2,5-dihydrotoluene after 4 F mol^{-1}.

Cathodic cleavage is useful for removal of protecting groups and in some cases has advantages over other methods. Such reactions have been reviewed [74] and most reactants were electroactive within the "potential window". In some cases deprotection was achieved at potentials close to the electrolyte decomposition, indicating the possible involvement of TAA-mercury. For example, removal of trityl [75], benzylidene [76] and benzyloxycarbonyl [77] was achieved at E < —2.8 V(SCE), and sample reactions are shown below.

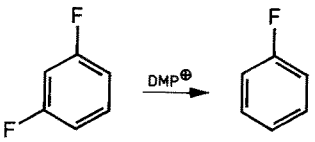


Cathodic cleavage of chlorides, bromides and iodides has been extensively studied [78], but only few examples of C—F bond cleavage have been reported. Cyclic voltammetry at 0.4 V s^{-1} showed [79] that in DMF with 0.1 M $(C_4H_9)_4NI$, benzotrifluoride exhibits a peak at —2.61 V(SCE) but α,α-difluorotoluene and α-fluorotoluene react

close to the discharge of the electrolyte (—2.83 and —2.84 V(SCE) respectively). Preparative electrolysis of benzotrifluoride (with stepwise increasing potentials) proceeded to cleave one, two or three fluorines, depending on the amount of charge transferred. The yields of the major products were 75% α,α-difluorotoluene (2.4 F mol^{-1}), 47% α-fluorotoluene (4.4 F mol^{-1}) and 90% toluene (8 F mol^{-1}).

Fluorobenzene is reduced at very negative potentials and it does not show a CV reduction peak discernible from the discharge of $(C_4H_9)_4N^+$. It exhibits a polarographic wave [80] at —30 °C at —2.97 V(SCE) in DMF-0.2 M $(C_4H_9)_4NPF_6$. Using mediated electron transfer to fluorobenzene, by five homogeneous redox catalysts (0.1 M $(C_4H_9)_4NI$ in DMF), E° for $C_6H_5F/[C_6H_5F]^-$ was estimated [81] as —2.97 V (SCE). Preparative electrolyses of fluorobenzene [18] were carried out in diglyme-0.5% H_2O with 0.1 M $(C_4H_9)_4NBF_4$, at a constant current. The reduction potential was —3.0 to —3.1 V(SCE) and after transfer of 2 F mol^{-1} the yield of benzene was 72%. Interestingly, the reduction of fluorobenzene could be catalyzed[8] by DMP^+. Catalysis was observed by CV, as shown for cyclohexanone in Sect. 1. When 0.01 M $(DMP)BF_4$ was present in solution, the reduction potential was —2.7 V(SCE) and, after transfer of 2 F mol^{-1}, 76% benzene was formed.

1,3-Difluorobenzene is more reactive than fluorobenzene. It shows a polarographic wave [83] in DMF, close to the discharge of $(C_4H_9)_4N^+$, $E_{1/2}$ = —2.82 V(SCE). It was preparatively reduced [18] at a constant current in diglyme-0.5% H_2O with 0.1 M $(C_4H_9)_4NBF_4$. The reduction potential during electrolysis was —2.8 V(SCE) and the



main product was fluorobenzene. Under these conditions some benzene was also formed and the process was not efficient. After transfer of 2 F mol^{-1} the products were 63% fluorobenzene, 3% benzene and 25% unreacted substrate. The reduction of 1,3-difluorobenzene could also be catalyzed by DMP^+. This was demonstrated by CV and in the presence of 0.01 M $(DMP)BF_4$ reduction could be carried out at —2.7 V(SCE). The DMP^+ catalyzed process was more efficient and resulted in selective cleavage of one fluorine only. After transfer of 2 F mol^{-1} fluorobenzene was obtained in 85% yield and only 9% reactant remained. No benzene was detected in the electrolysis mixture.

8 Aliphatic Ketones

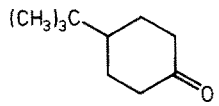
Aliphatic ketones, in general, do not exhibit well defined reduction waves or peaks within the "potential window" of aprotic solvents. Their reduction is strongly affected by protons, due to the protonation steps involved, and most electrochemical measure-

8 It is noteworthy that although DMP^+ catalyzes reduction of fluorobenzene it does not affect benzene. The respective electron affinities in the gas phase are —0.89 and —1.15 eV [27] and reaction of fluorobenzene with hydrated electrons is only 6 times faster than that of benzene [82].

ments have therefore been performed in protic media. For example, in dry DMF containing $(C_4H_9)_4N^+$ electrolytes the reduction of acetone, cyclopentanone and cyclohexanone overlaps with background decomposition. In ethanol-4% H_2O they exhibit reduction waves with the respective $E_{1/2}$ of −2.57, −2.46 and −2.40 V (SCE) [84].

Acetone has been extensively studied in aqueous acidic solutions, where protonation precedes the electrochemical step. In basic solutions, containing various alkali metal hydroxides or $(CH_3)_4NOH$ as the supporting electrolyte, it was shown [85] that dimerization to pinacol is more effective in solutions containing $(CH_3)_4N^+$ than in Li^+, Na^+, K^+ or Cs^+ hydroxides. In alcoholic solution of $(CH_3)_4NCl$, acetone was reduced [13] at a constant potential and isopropanol (50%) was reported as the product. Although the possibility was not discussed it could be that pinacol was a significant byproduct. This could certainly explain the low material balance observed.

Preparative reduction [86] of the alkylcyclohexanones *61*, *62* and *63* has been carried out at a constant current in solution of 0.1 M $(C_4H_9)_4NI$. The reactions proceeded



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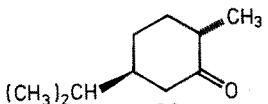

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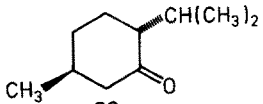
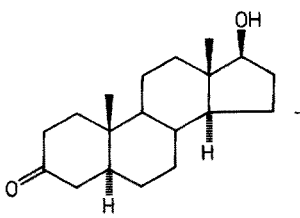


63

with low current efficienty (15–37%). The major products of *61* and *62* were the corresponding alcohols with the equatorial isomers predominating. The ratio of the equatorial/axial alcohols obtained from *61* was 77/15 and from *62* 97/3. The behavior of *63* was different, probably due to steric hindrance, and the major product was the corresponding hydrocarbon.

Kabasakalian and coworkers [87] have achieved the cathodic reduction of steroidal ketones in ethanol-20% H_2O with 0.2 M $(C_4H_9)_4NCl$ as the supporting electrolyte. The reactions proceeded with very high chemical yield and were rather stereoselective. Electrolysis of androstane-17β-ol-3-one (*64*) at −2.6 V(SCE) gave the 3β-equatorial alcohol *65* quantitatively. Under identical conditions the exocyclic carbonyl of *66* was also reduced and the corresponding alcohol was obtained in 92% yield. But, the reaction was less stereoselective and the ratio of the 20β-/20α epimers was 74/26.



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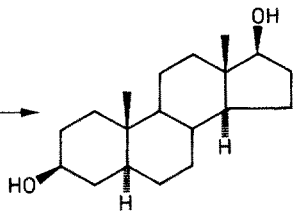

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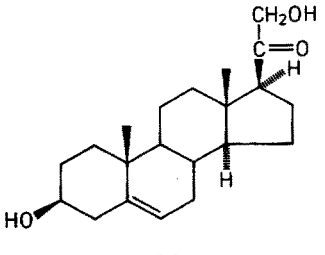

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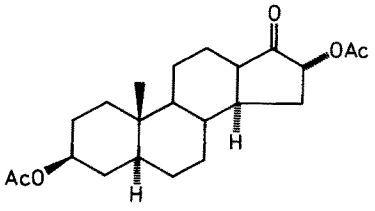
Electrolysis [87] of the diacetate *67* under conditions as those used for *64* formed exclusively *65* (95%). Thus at −2.6 V(SCE) both the acetate at C-16 was reductively cleaved and the carbonyl was reduced (the acetate in the 3-position was hydrolyzed,

due to the basic conditions during electrolyis). Since reductive cleavage of acetate α to carbonyl should be easier than reduction of a cyclopentanone [the respective potentials measured [84] in DMF-4% H_2O were −1.99 and −2.43 V(SCE)], an attempt was



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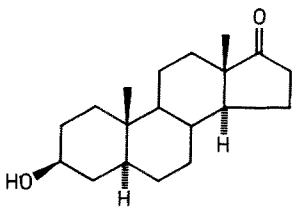

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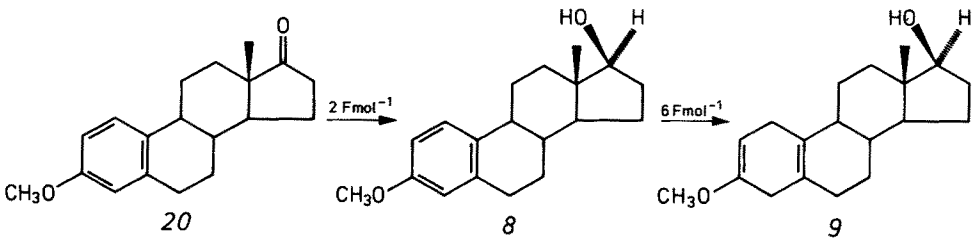
made to selectively cleave the C-16 acetate. Reduction of *67* at −2.1 V(SCE) was not selective, however, and a mixture of *68* and *65* was obtained in a 57/43 ratio.

The following example demonstrates that by proper control of the current and the amount of charge transferred, the cathodic method can be successfully used for selective reaction of a molecule containing more than one reducible functional group. Estrone-3-methylether (*20*) contains a carbonyl function and a benzene moiety. Electrolysis at constant current in THF-8% H_2O containing 0.5 M $(C_4H_9)_4NBF_4$ yielded *8* or *9* as the major product, depending on the amount of charge transferred [11].



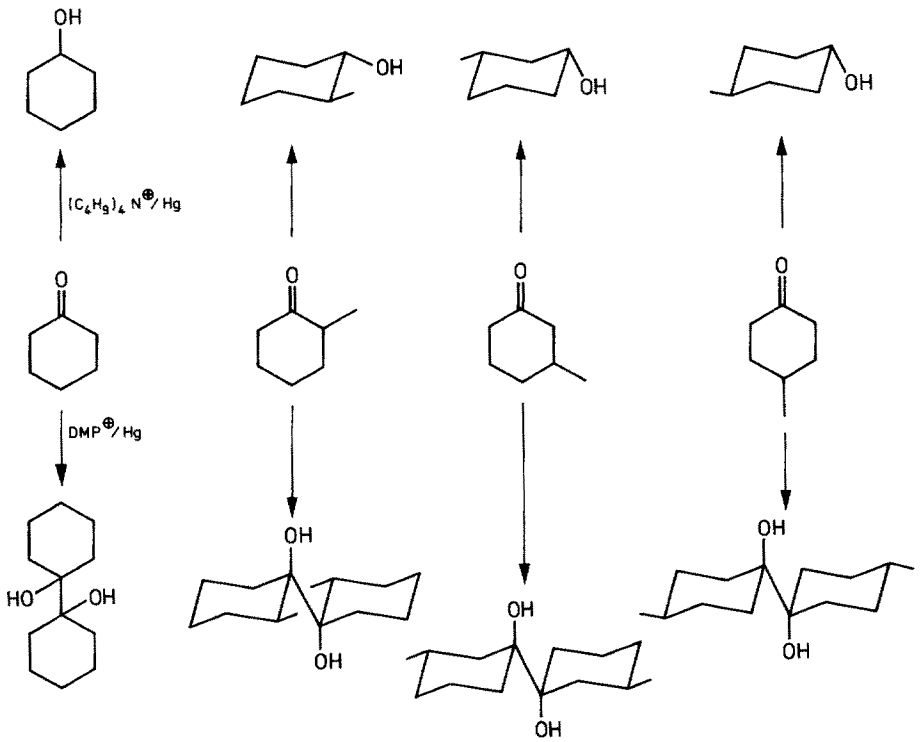
20 *8* *9*

With 2 F mol^{-1} the more reactive carbonyl was reduced and *8* was formed. Consequently the benzene reacted and after transfer of 6 F mol^{-1} *9* is obtained in good yield. Reduction of *20* at lower current density are more selective and purer products are formed. At 16 mA cm^{-2} the product composition after transfer of 2 F mol^{-1} was: 76% *8*, 8% *9* and 16% *20*, and after 6 F mol^{-1}: 14% *8* and 86% *9*. At 8 mA cm^{-2} the yield of *8* was >95% after transfer of 2 F mol^{-1} and after transfer of 6 F mol^{-1} *9* was obtained in a yield of 92%.

A study on the reduction of aliphatic ketones, which contributed to understanding the mechanism and provided some examples of synthetic interest, has been in progress in our laboratory. It has involved the reduction of aliphatic ketones in organic solvents with $(C_4H_9)_4NBF_4$ as the electrolyte and dimethylpyrrolidinium (DMP^+) in small concentrations as the catalyst. Most of the substrates listed below do not exhibit reduction waves or peaks in the "potential window". The reduction of all the substrates can be catalyzed by DMP^+ and in the presence of the catalyst preparative reductions could be carried out at potentials at which the substrates are otherwise electroinactive. Catalysis was also ascertained with CV and polarographic measurements like those described in the introduction for cyclohexanone. Product analysis

demonstrated that the DMP^+ mediated process results in $1\,e^-$ transfer, while in its absence $2\,e^-$ transfer products are common.

Cyclohexanone and the three methyl cyclohexanones were reduced [16,17] in DMF or diglyme-0.5% H_2O with 0.1 M $(C_4H_9)_4NBF_4$ as the electrolyte; at a constant potential of −2.95 V(SCE). The amount of charge consumed for complete consumption of the reactants was 2.2 F mol^{-1} and the corresponding alcohols were formed in reasonable yield (60–75%). The reaction was stereoselective and only the isomers



with both methyl and hydroxyl at the equatorial positions were obtained. When 0.005 M $(DMP)BF_4$ was added, electrolysis could be carried out at −2.70 V(SCE). The reactants were completely consumed after transfer of 1.1. F mol^{-1} and the corresponding pinacols were the only products. In this case also, only the more stable diequatorial isomers were formed.

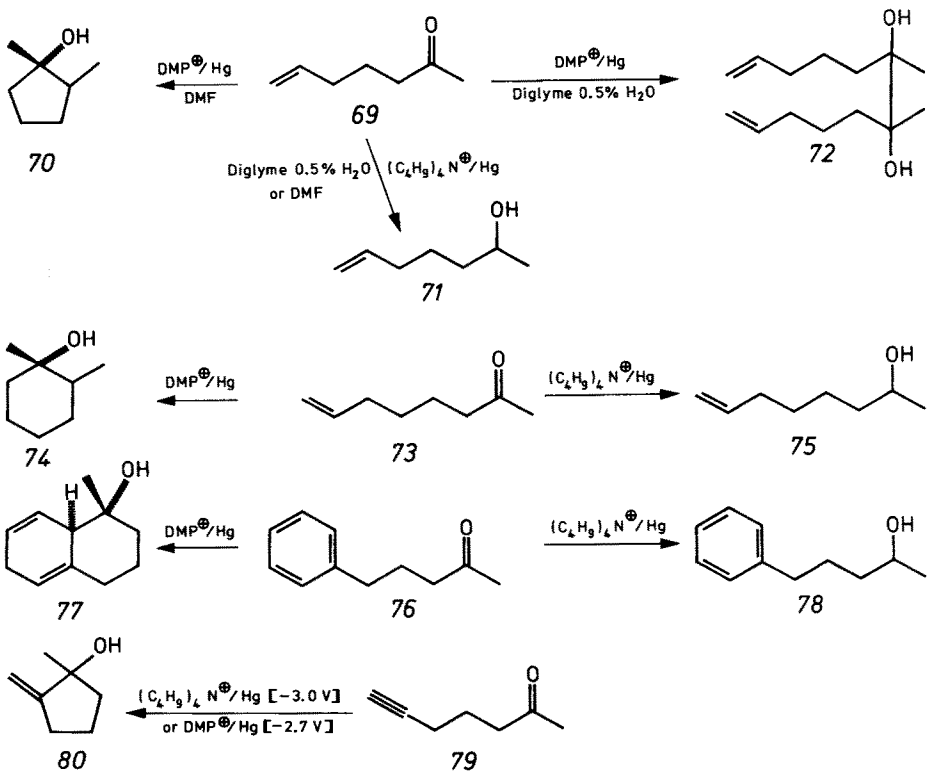
The unusual ability of DMP^+ to promote the formation of $1\,e^-$ products, prompted attempts to use this catalyst for transformations other than pinacolization. The examples chosen were aimed at $1\,e^-$ reductive intramolecular cyclizations. Shono and co-workers [88] have reported such cyclizations at graphite and Sn cathodes. Their experiments were carried at a constant current in concentrated solutions of $(C_2H_5)_4N^+$ electrolytes. The substrates used should have, in principle, been electroinactive within the "potential window". It was therefore feasible to assume the intermediacy of $(C_2H_5)_4N$-metal and it seemed that $DMP^+(Hg_5)^-$ might be a more efficient and predictable catalyst for reductive cyclization. The study was fruitful. Shono-type cyclizations were achieved at Hg cathodes with DMP^+ as the catalyst. Unlike at

Table 10. Intramolecular Reductive Cyclization of Aliphatic Ketones [16, 17]; 0.1 M $(C_4H_9)_4NBF_4$ in DMF, 2 F mol^{-1}

Substrate	Catalyst [0.005 M]	E [V (SCE)]	Product (yield)
69	none	−3.10	*71* (85%)
69	$(DMP)BF_4$	−2.70	*70* (98%)
73	none	−3.00	*74* (35%), *75* (45%)
73	$(DMP)BF_4$	−2.70	*74* (72%)
76	none	−3.00	*77* (10%), *78* (80%)
76	$(DMP)BF_4$	−2.70	*77* (80%)
79	none	−3.00	*80* (80%)
79	$(DMP)BF_4$	−2.70	*80* (80%)

graphite and Sn, the reactions proceeded with high current efficiency, the reaction mechanism was clarified and shown to involve $DMP^+(Hg_5)^-$ as the mediator for electron-transfer.

The substrates *69*, *73*, *76* and *79* were chosen [16, 17] to test the possibility of forming five and six-membered rings and of cyclizing carbonyls onto alkene, alkyne and benzenoid moieties. Reductions were carried out with DMP^+ as the catalyst and without it, and the results are shown in Table 10. In the absence of DMP^+ reduction

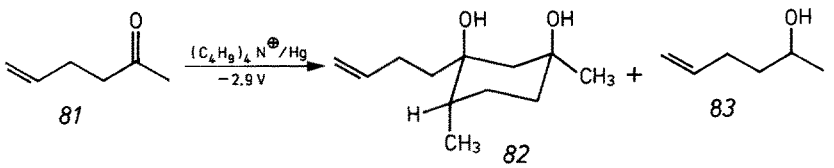


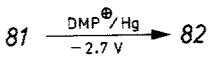
took place around —3 V(SCE) while in its presence it could be carried out at —2.7, 0.3 V more positive. In solutions with DMP^+ *69*, *73* and *76* formed cyclic alcohols exclusively, while in its absence *69* yielded the simple straight chain alcohol and *73* and *76* gave mixtures of cyclized and non-cyclized products. The reduction of *79* was different. Although catalyzed by DMP^+, as evidenced by the potential, the cyclic product *80* was obtained with or without DMP^+ in solution. The DMP^+ mediated reductive cyclizations are useful. They are stereoselective and provide one isomer almost exclusively. The cyclic alcohols are formed with high chemical yield and current-efficiency, and their purification is simple due to the lack of interferring byproducts.

To examine whether TAA^+ cations other than DMP^+ can catalyze intramolecular reductive cyclizations, the reduction of *69* was performed with 0.005 M $(C_2H_5)_4NBF_4$ in solution. Like DMP^+, $(C_2H_5)_4N^+$ had a catalytic effect, *69* could be reduced at —2.80 V(SCE) and the cyclic alcohol *70* was obtained in high yield (94%). However, $(C_2H_5)_4N^+$ was less efficient and 6 F mol^{-1} were consumed for completion, while the DMP^+ mediated reduction of *69* was complete after transfer of 2 F mol^{-1}.

Realizing that protonation steps are important, reductions of *69* were performed in diglyme-0.5% H_2O. Like in DMF, in the absence of catalyst the potential was —3.10 V and the simple alcohol *71* was the only product (86%). The DMP^+ mediated reduction, however, was different in this solvent. It took place at the same potential —2.70 V (SCE), but the reactant was consumed after only 1 F mol^{-1} and the correspoonding pinacol *72* was the only product (60% after repeated recrystallizations).

An interesting transformation which involves dimerization and cyclization was discovered when the γ-enone *81* was reductively converted to *82*. The mechanism of this dimerization-cyclization is yet to be elucidated. It involves two molecules of reactant, reduction and some aldol type condensation. The process is catalyzed by DMP^+ and proceeds with high stereoselectivity yielding a single isomer.





Dimerization-cyclization of *81* was significant in DMF with 0.1 M $(C_4H_9)_4NBF_4$ at —2.9 V(SCE). However, under these conditions some simple alcohol *83* was also formed and the composition of the electrolysis product was 75% *82* and 20% *83*. DMP^+ catalyzed this reduction and upon addition of 0.005 M $(DMP)BF_4$ *81* could be reduced at —2.70 V(SCE). The DMP^+ mediated reduction yielded only *82* (80% isolated pure product).

9 Summary

The studies described above demonstrate that a number of types of compounds, both aliphatic and aromatic, are cathodically reduced in the potential region —2.7 to —3.1 V(SCE) at mercury in a suitable solvent containing a TAA^+ electrolyte. It

seems likely that other types of compounds will also reduce in this potential region and it is certain that more examples will be found within the functional group types already discovered.

The observation that so many compounds reduce in such a narrow potential range is curious. We hypothesize that one reason is that many of these reactions are catalyzed via the TAA^+/TAA-mercury couple. The mediated reactions then include reduction of compounds, like benzene, whose E° for single electron transfer is more negative than —3.1 V(SCE). A second reason for the possibility of reducing many compounds in this narrow potential range is that the reduction rates often depend on proton availability, which can be adjusted to make the process feasible.

Another curious observation is that many of the reactions described are rather selective and proceed with relatively high chemical and electrical yields. In general, it is believed that high energy processes are unselective. Reactions at very negative potentials should be, therefore, rather unselective. Furthermore, this potential range is one where the electrolyte and electrode are not inert. It seems that the "background decomposition" reaction is a very selective one generating TAA-mercury and it seems that TAA-mercury react rapidly and specifically with the organic substrates. We do provide a note of caution because the recovery of TAA^+ after bulk electrolysis has not been satisfactorily investigated, but the selectivity of organic reductions is remarkable. Especially remarkable is the selectivity exhibited when two different functional groups are present in the molecule, each of which can be reduced in this potential range. Several of these examples show that the electrochemical method is easily tuned to give better results than the alkali metal-ammonia alternative.

Quite unpredicted was the dependence of product structure on the structure of the TAA^+ used for the reaction. Even though the hypothesized TAA-mercury provides a mechanistic paradigm to understand this selectivity, it is still surprising when one considers the small change in structure of TAA^+ and the narrow potential range. There are too few examples to generalize from, but a suggested explanation is that the smaller, more easily reduced TAA^+ are weaker reducing agents and they favor one-electron processes over two-electron ones, e.g. pinacol over alcohol. This requires a fortuitously delicate balance of electron transfer and chemical rates. Obviously central to this problem are the insoluble TAA-mercury. This review has not detailed the few studies which have explored TAA^+ electrochemistry. It is a fascinating story, which is only now slowly unfolding.

For the future it seems clear that this field is open to many fruitful investigations and developments. The creative organic chemist will develop more complex and more useful syntheses and the electrochemist will bring quantitative understanding to the mechanism(s) of this unusual, general and selective heterogeneous catalytic process. Because it is possible to obtain TAA-metals from metals other than mercury, the range of observed reactions may increase phenomenally — and in an understandable way. Indeed, this entire field is ripe for further discovery, better understanding and more useful applications.

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Synthesis of Alkaloidal Compounds Using an Electrochemical Reaction as a Key Step

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Table of Contents

This review describes application of electroorganic reactions to synthesis of some key skeletons which are commonly found in natural alkaloids and some key intermediates which are useful materials for formation of the alkaloidal structures. The methods of synthesis are classified into three categories, namely, (1) Oxidative coupling, (2) Oxidative activation of the position α to the nitrogen atom of amines and (3) Reductive addition and substitution. In the first category, inter- and intra-molecular couplings of phenols and phenolic ethers and their application to synthesis of morphinandienone type alkaloids are mainly described. The second category is devoted to the anodic activation and subsequent carbon-carbon bond forming reactions at the position α to the nitrogen atom of amines. A variety of nitrogen heterocycles including quinoline, pyrrolizidine, indolizidine and quinolizidine skeletons are synthesized by using this methodology. In the third category, formation of active species by cathodic reduction of alkyl or aryl halides and their addition to unsaturated systems such as aromatic nucleus and carbonyl groups are mentioned. Optically active pyrrolizidine and indolizidine skeletons are obtained by this method. Reductive formation of anionic active species is also achievable by cathodic reduction of iminium salts. The successful application of substitution reaction between this active species and benzyl halides to the synthesis of indole and isoquinoline alkaloids is also contained in the third category.

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1 Introduction

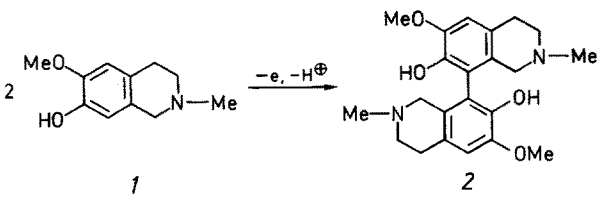
Although electroorganic reactions seem to be useful tools for the transformation of amine derivatives, their application to the total synthesis of natural alkaloids themselves has not always been extensively studied.

Therefore, this review is mainly devoted to the application of electroorganic reactions to the synthesis of some key skeletons which are commonly found in natural alkaloids and some key intermediates which are useful materials for the formation of alkaloidal structures. The synthesis of some other nitrogen heterocycles which are usually not found in alkaloidal compounds will not be part of this review even though the structures are highly interesting as targets in organic synthesis.

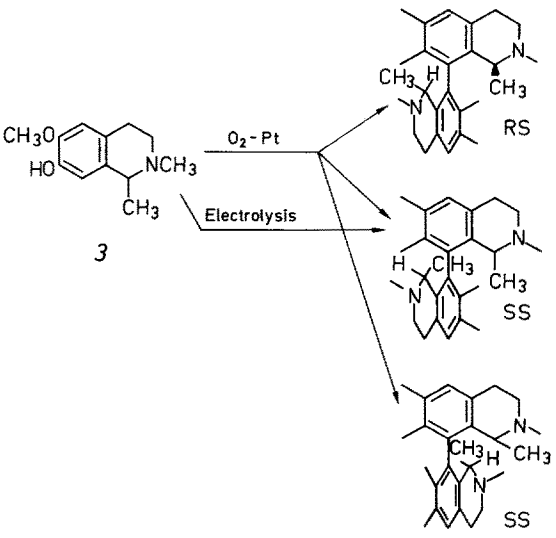
This review is classified according to the type of the key reaction, but not to the type of the alkaloid. It contains not only the application of the reactions but also brief explanations of some fundamental aspects of the reactions.

2 Oxidative Coupling

One of the most reliable electrochemical methods for the synthesis of alkaloidal skeletons is the oxidative coupling of phenolic and related compounds. A typical early example is the oxidative coupling of corypalline *1* to its dimer *2* [1].



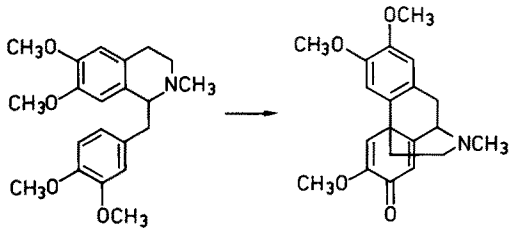
1 *2*



3

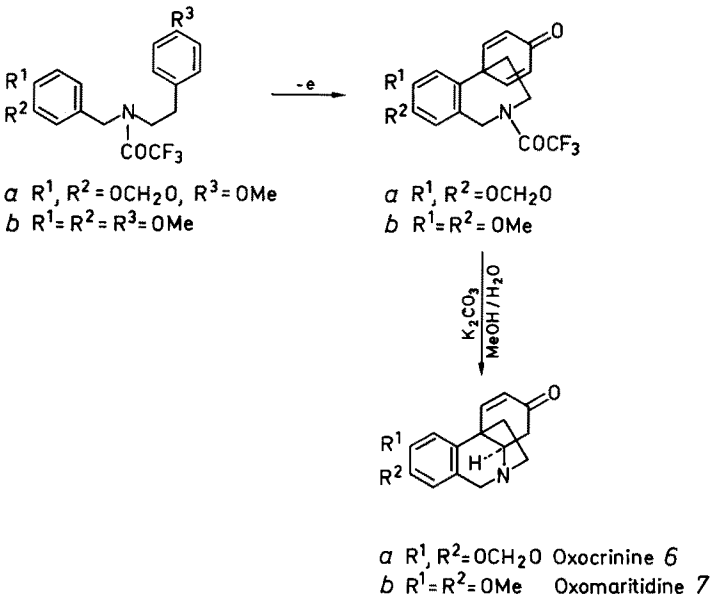
The interesting character of the electrooxidative coupling is its stereoselectivity. The anodic dimerization of racemic 1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline *3*, for instance, gives one single isomer, whereas platinum catalyzed oxygenation forms all three isomers of the carbon-carbon dimer. In the anodic dimerization, coupling occurs only between molecules of identical configuration, and only one of two possible rotational isomers is formed [2]. The optimum conditions for the coupling of these phenols have been suggested to be oxidation of their sodium salts in CH_3CN using Et_4NClO_4 as supporting electrolyte at a graphite felt anode [3].

Although the anodic intermolecular coupling of phenols gives quite satisfactory results, the corresponding intramolecular coupling is not always successful [4]. On the other hand, the electrochemical oxidation of phenol ethers has been extensively studied and it has been found that the intramolecular carbon-carbon coupling takes place satisfactorily. The first typical reaction is the anodic intramolecular coupling of laudanosine *4* to yield O-methylflavinantine *5* [5].



4 *5*

This oxidation was carried out at 1.1 V and 0 °C using a three compartment cell equipped with platinum electrodes. The solvent system is purified acetonitrile contain-

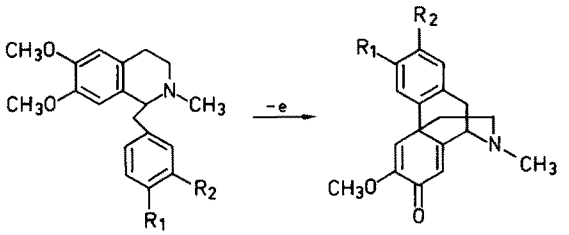


a $R^1, R^2 = OCH_2O$, $R^3 = OMe$
b $R^1 = R^2 = R^3 = OMe$

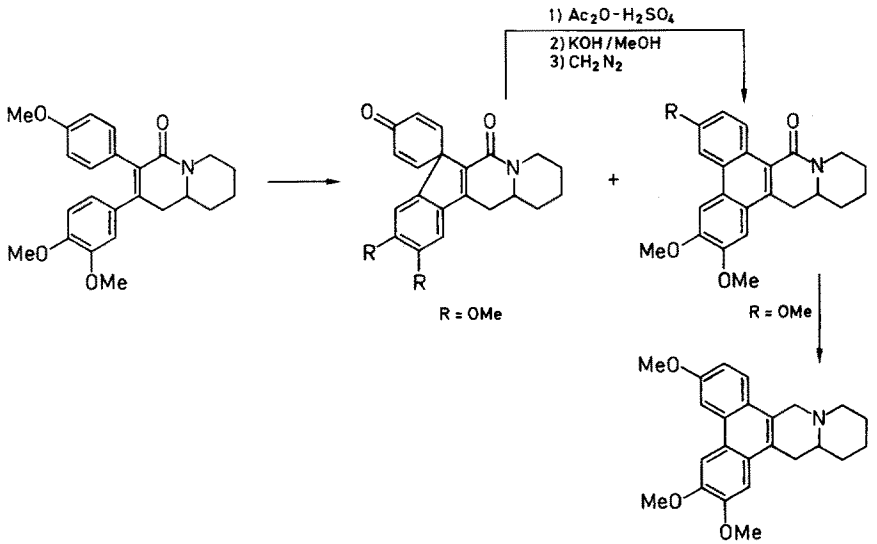
a $R^1, R^2 = OCH_2O$
b $R^1 = R^2 = OMe$

a $R^1, R^2 = OCH_2O$ Oxocrinine *6*
b $R^1 = R^2 = OMe$ Oxomaritidine *7*

ing Na_2CO_3 and Me_4NBF_4 or $LiClO_4$. This anodic coupling has been also applied to the synthesis of oxocrinine *6*, oxomaritidine *7*, amurine *8* and pallidine *9*. It has been found that using HBF_4 (0.1 M) as the electrolyte gives better results [6]. Cryptopleurine *10*, the alkaloid having the ring structure of phenanthro-quinolizidine system, has synthesized by using a similar method [7].



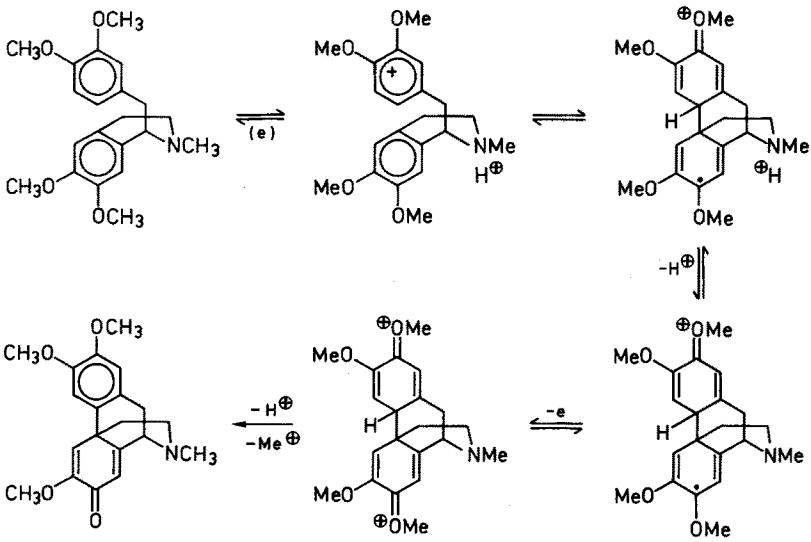
$R_1 = OCH_3$; $R_2 = OH$ Pallidine *9*
$R_1, R_2 = -OCH_2O-$ Amurine *8*



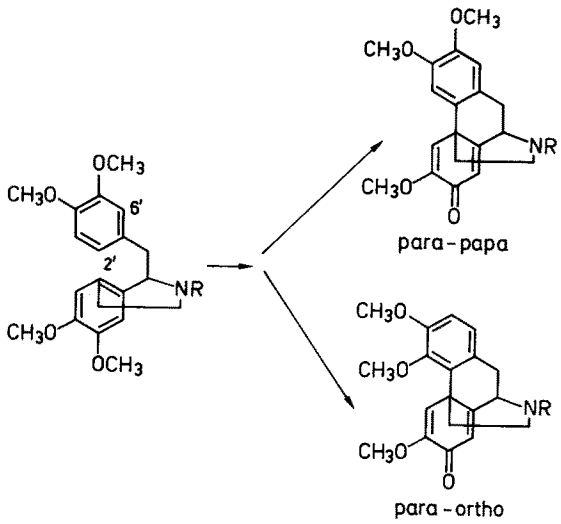
Cryptopleurine *10*

The mechanism of the anodic intramolecular coupling of 1-benzyltetrahydroisoquinoline type compounds to the corresponding morphinandienone alkaloids is not always simple. Especially, the mechanism of reactions carried out under nonacidic conditions can not be correctly described since the low yields of the cyclized products make the mechanism ambiguous. The mechanism under acidic conditions has been studied extensively. There are two possible routes for the initiation step. One is the oxidation of the aromatic ring system, and the other is the removal of one nonbonding electron from the amino nitrogen atom. The possibility of the latter route is, however very low since the non-bonding electrons are blocked by protonation. This is proved by the observation that the intramolecularly coupled product obtained from 1-deuterated O-benzyl-pseudo-codamine retained more than 95% of deuterium and

hence deprotonation α to the nitrogen is not involved in the initial oxidation. The most probable route is shown in Scheme 1, in which three reversible steps are followed by the rate determing solution electron transfer [8].

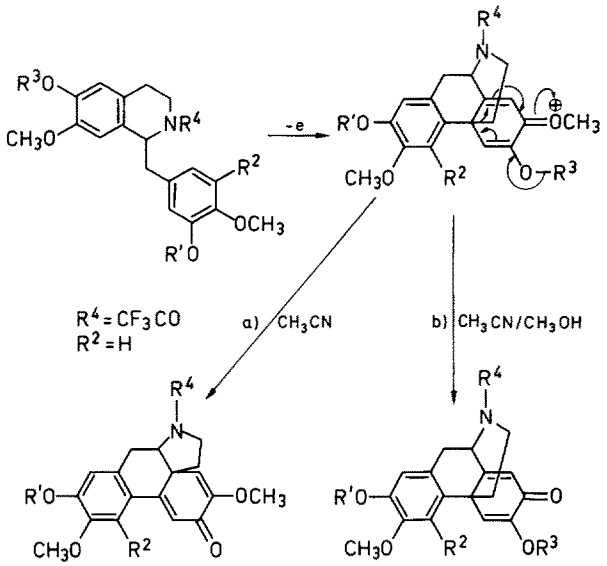


All the anodic intramolecular coupling of 1-benzyltetrahydroisoquinolines give the flavinantine type products via coupling at the 2′ position (para-para coupling), whereas the coupling at 6′ position (para-ortho coupling) is obviously more desirable since it provides products with morphine type substitution pattern. Quite a variety of modifications have been carried out to prevent the para-para coupling and to favour the para-ortho coupling. Using halogen substituents on 2′ or 3′ position of the benzyl



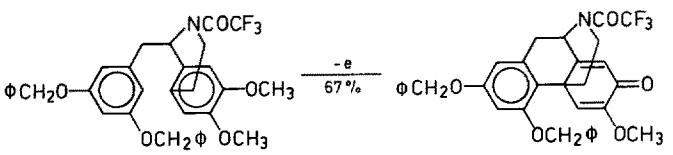
ring as blocking groups was not successful, as cleavage or substitution products were obtained [9].

The use of 2′-nitro or 2′-N-acetylamino substituents leads to cleavage at C-1. The trifluoroacetylation of amino group, however, changed the course of the reaction and the products were not morphinandienones but neospirodienones. This change of the reaction course may be initiated by rearrangement of the intermediate morphinandienone-type cation. The addition of methanol to the reaction system as a nucleophile, however, makes it possible to trap the intermediate cation before its rearrangement. But the para-para coupling pattern is retained [10].

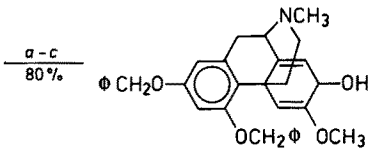


Finally, a 1-(3,5-dibenzyloxybenzyl)tetrahydroisoquinoline derivative has been synthesized as the starting compound, which has three prerequisites that should favour the intramolecular ortho-para coupling: both benzene rings are equally activated by alkoxy groups, the symmetrically substituted benzyl ring has two identical coupling sites at 2′ and 6′, and both coupling positions are activated by para alkoxy groups. The anodic oxidation of this starting compound *11* at 1.0 V in CH_3OH/CH_3CN (4:1) afforded in 66% yield the desired para-ortho coupling product *12*, which is easily transformed to salutaridinol *13* and 2-hydroxy-3-desoxythebaine *14* [11].

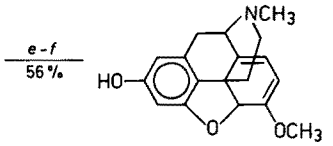
The anodic oxidation of 4-(3,4-dimethoxybenzyl)6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline does not afford the intramolecularly aryl-aryl coupled prod-



11 *12*



Salutaridinol *13*

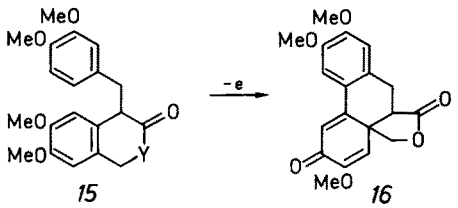


2-Hydroxy-3-desoxy-thebaine *14*

a: NaOH, MeOH; *b*: H_2CO, MeOH; *c*: $NaBH_4$, MeOH;
e: Li, NH_3; *f*: DMF $(OCH_2-)_2$ CH_2Cl_2

ucts but gives the corresponding 3,4-dihydroisoquinolinium and 4-(3,4-dimethoxybenzylidene)-6,7-dimethoxy-2-methyl-1,4-dihydroisoquinolinium salts [12].

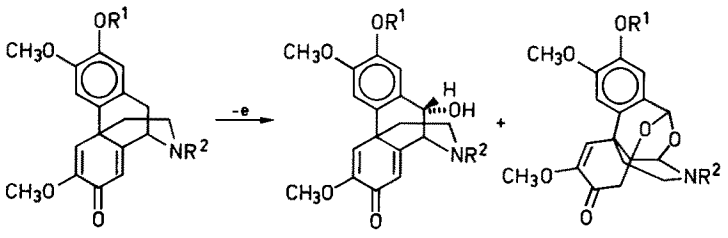
In connection with the anodic intramolecular coupling of 1-benzyltetrahydroisoquinoline derivatives, the anodic oxidation of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochromanone *15* has been studied rather extensively. The main product obtained from the isochromanone is a γ-lactone, 7a,8-dihydro-3,10,11-trimethoxy-2 H-phenanthro[9.8a, b]furan-2,7(5 H)-dione *16* [13].



15
Y=O

16

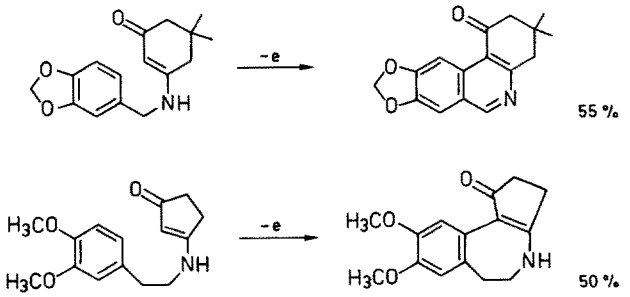
The morphinandienone alkaloids themselves can also be electrochemically oxidized. A cyclic voltammogram of morphinandienone (R^1, R^2 = CH_3) *17* in acetonitrile at platinum shows the anodic peaks at 1.15 V and 1.33 V vs. Ag/Ag^+. Its preparative anodic oxidation at 1.2 V in CH_3CN/0.2 M HBF_4 gives trans-10-hydroxy-O-methyl-



17 *18* *19*

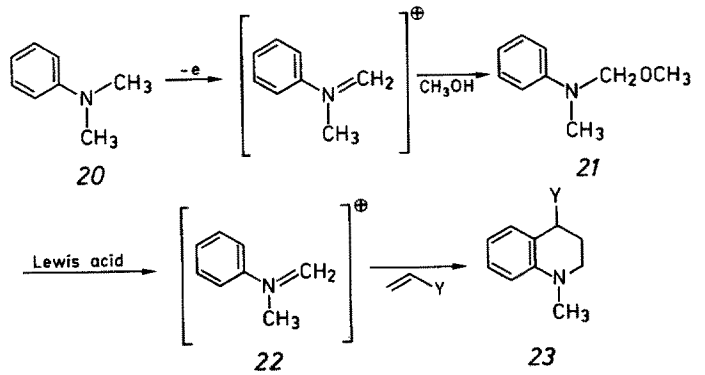
flavinantine *18* stereospecifically in 38% yield together with the cyclic acetal *19* in 37% yield. The latter product is formed by further oxidation of *18* [14].

Intramolecular coupling also takes place in the anodic oxidation of N-benzyl- and N-β-phenethyl-enaminoketones. The oxidation was carried out in 0.3 M $NaClO_4$/CH_3OH at 10 °C using an undivided cell and graphite electrodes [15].

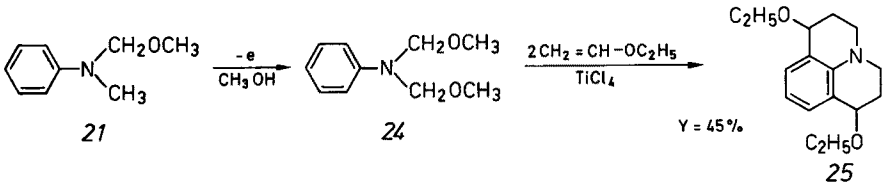


3 Oxidative Activation of the Position α to the Nitrogen Atom of Amines

Although the anodic generation of a cation in α-position to nigrogen in aliphatic amines is not difficult, this type of reaction is not always useful to the synthesis of alkaloidal compounds, since the cation is not stable and a simple dealkylation is the usual follow-up reaction. N-monomethyl and N,N-dimethylanilines are, however, useful starting materials for the synthesis of the skeleton of tetrahydroquinoline. The anodic methoxylation of N,N-dimethylaniline *20* takes place at the methyl group, and an iminium ion intermediate *22* is easily generated by treatment of the methoxylated product *21* with Lewis acid. This intermediate can be trapped in situ with a variety of nucleophiles such as electron-rich olefins yielding tetrahydroquinolines *23* [16].



Further anodic oxidation of the monomethoxylated compound in methanol gives N,N-bis(methoxymethyl)aniline *24*, which yields a julolidine derivative *25* upon reaction with two molecules of ethyl vinyl ether.



21 24 25

As described above, the anodic oxidation is not always a useful technique to activate the position α to the nitrogen atom of aliphatic amines.

On the other hand, a similar activation has been found to be practically possible when carbamates or amides instead of amines themselves are used as the starting materials. The α cation formed from carbamates and amides is sufficiently stable to be trapped by nucleophiles in solution [17].

$$RCH_2-\underset{R'}{N}-YZ \xrightarrow{-e} RCH_2-\overset{+\cdot}{\underset{R'}{N}}-YZ \xrightarrow{-e} \xrightarrow[-H^{\cdot}]{} R\overset{+}{C}H-\underset{R'}{N}-YZ$$

$$\xrightarrow{SH} R\underset{S}{C}H-\underset{R'}{N}-YZ$$

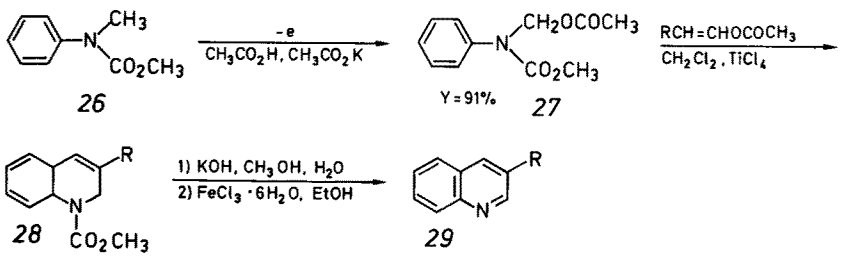
SH: solvent (CH_3OH, CH_3CO_2H, etc.), Y: CO, PO, or SO_2, Z: R'' or OR''

When the α cation is formed in methanol or acetic acid, for instance, a methoxy or acethoxy group is introduced to the α position, and the product is a useful reagent for the amidoalkylation as shown below in a general scheme.

$$R^1CON\underset{R^3}{\overset{R^2}{C}}HOCH_3 \rightarrow R^1CO\overset{+}{\underset{R^2}{N}}=CHR^3 \xrightarrow[Nu]{} R^1CON(Nu)-CHR^3$$

The amidoalkylation is conveniently applicable to the synthesis of alkaloid type compounds. Some examples are shown below.

By transformation of N-monomethylaniline to a carbamate *26* as the starting compound, instead of the tetrahydroquinoline *23* the quinoline skeleton *29* can be prepared as shown in the following route. The carbamate *26* then is acetoxylated at



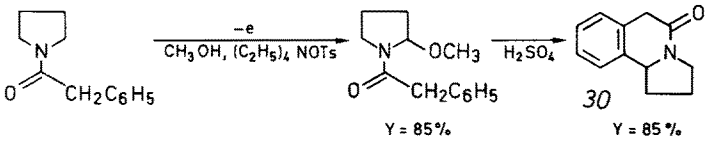
26 Y = 91% 27

28 Y = 65% (R = C_3H_7)
Y = 59% (R = i-C_3H_7)

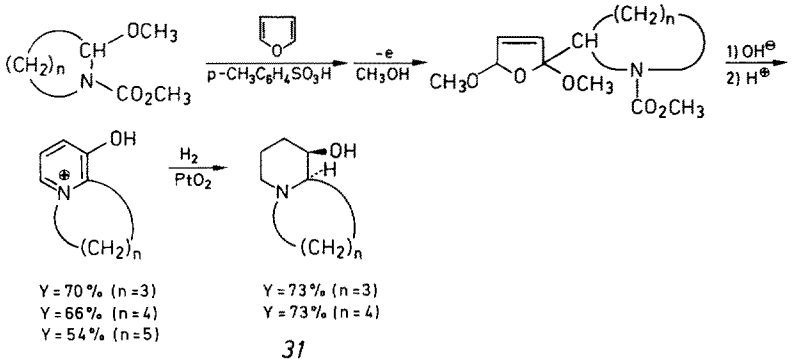
29 Y = 69% (R = C_3H_7)
Y = 67% (R = i-C_3H_7)

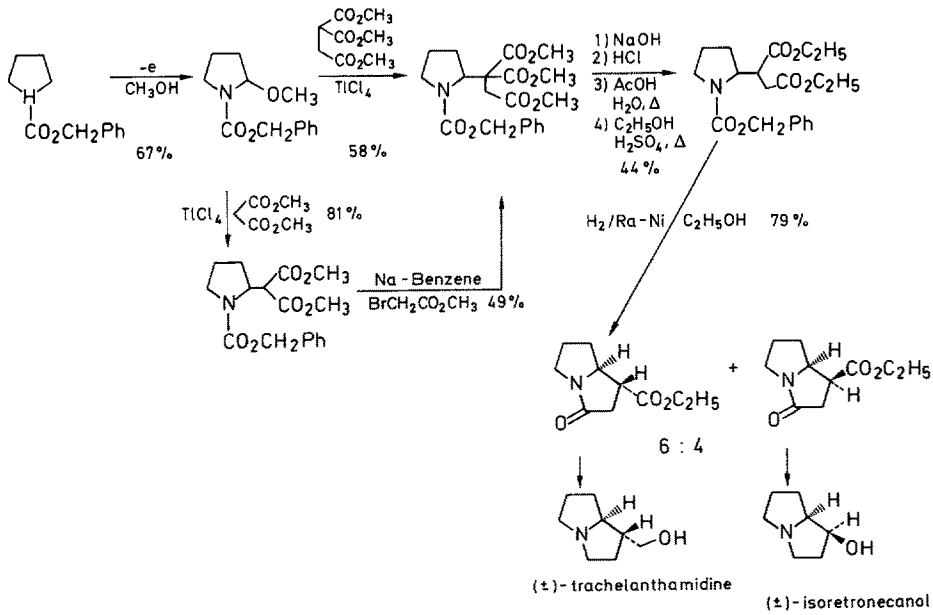
the methyl group by anodic oxidation to give *27* [18]. Reaction with vinyl acetates in presence of Lewis acids yields *28* which then is deprotected and oxidized to *29*.

An isoquinoline derivative *30* has been prepared by an intramolecular electrophilic substitution between the N-acyliminium ion and a phenyl group [19].

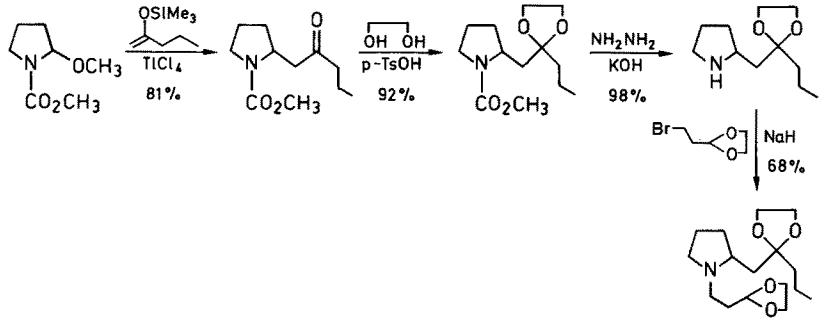


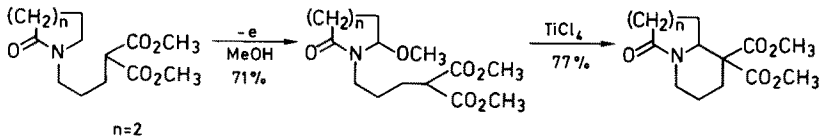
The synthesis of 1-azabicyclo[4.n.0] systems *31* has also been carried out by using a similar substitution between heteroaromatic rings such as furan and the N-acyliminium ion as the key reaction [20].

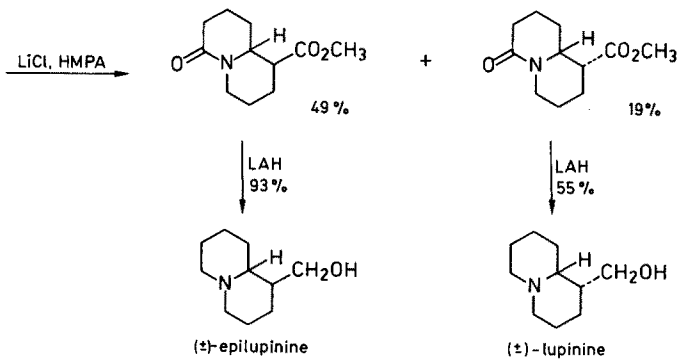




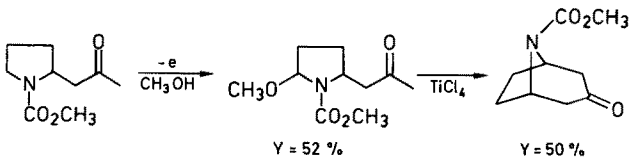
Trapping of the α-cation by active methylene compounds or enol ethers has been applied to the synthesis of some alkaloids having the skeletons of pyrrolizidine, indolizidine, and quinolizidine [21–23].





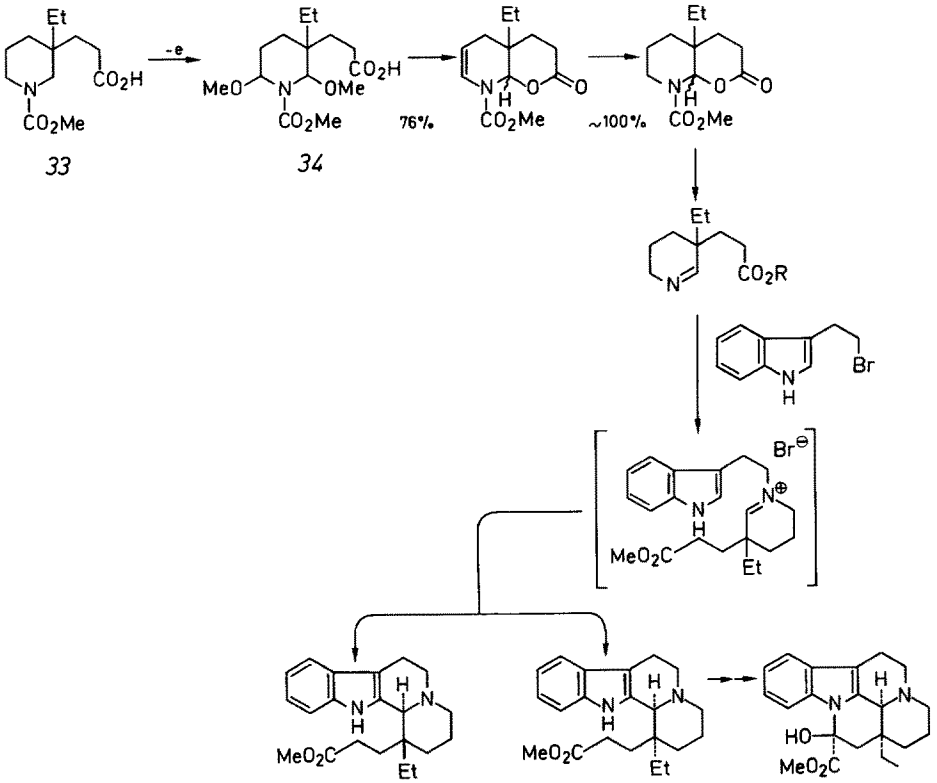


An intramolecular trapping of the intermediate α-cation by an enol of a ketone moiety has been applied to the formation of the tropanone skeletone *32* [19].



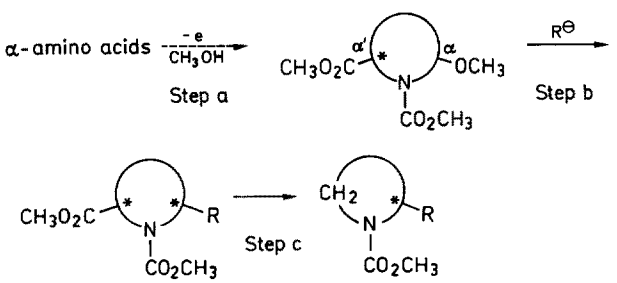
32

A key intermediate for the synthesis of the indole alkaloid, vincamine, has been prepared by the anodic oxidation of 1-carbomethoxy-3-ethyl-3-(β-carboxyethyl)-piperidine *33* in methanol. The regioselective methoxylation at the 2-position was not possible, instead the 6-position was also methoxylated. Thus, the starting material has been methoxylated at both 2- and 6-positions to give *34* and the methoxy group on the 6-position is eliminated during the formation of lactone ring at the 2-position [24].



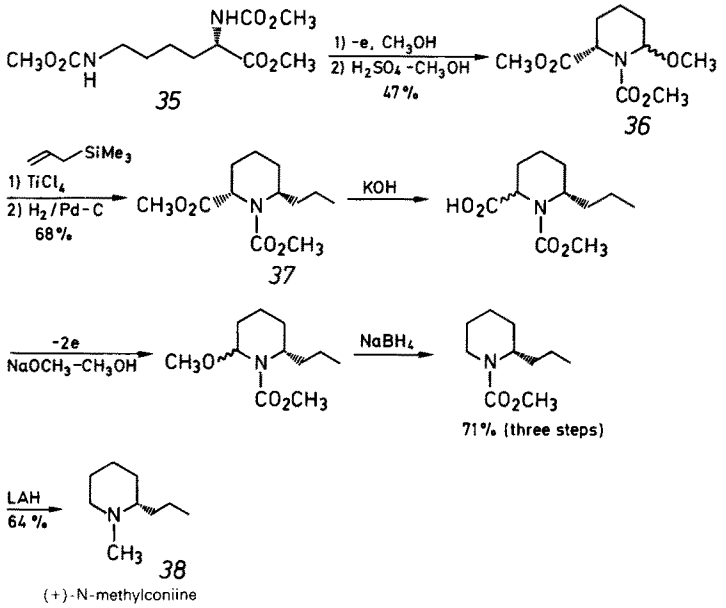
Optically active alkaloids may be synthesized by using a diastereoselective introduction of a substituent to the intermediate α-cation as it is exemplified by the synthesis of optically active (+)-N-methylconiine [25].

The methodology used in this synthesis is that (a) the chiral starting compounds



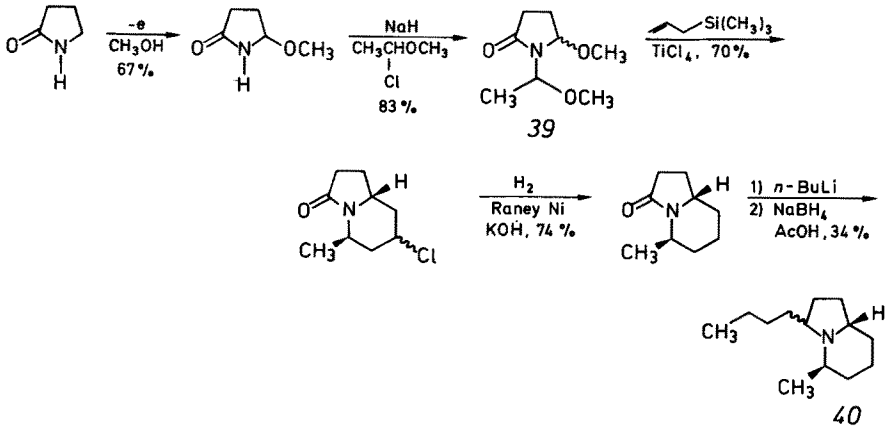
are prepared from α-amino acids using anodic methoxylation, (b) the substituent R is diastereoselectively introduced to the α-position under the influence of the alkoxycarbonyl group on the chiral α′-position and (c) finally, the alkoxycarbonyl group is eliminated after R is introduced.

The synthesis of N-methylconiine *38* from the biscarbamate of L-lysine *35* is shown below.



The reaction of the methoxylated intermediate with allyltrimethylsilane followed by hydrogenation gave the cis-disubstituted compound *37* exclusively. The same methodology has also been applied to the synthesis of optically active Sedamine from L-lysine [26].

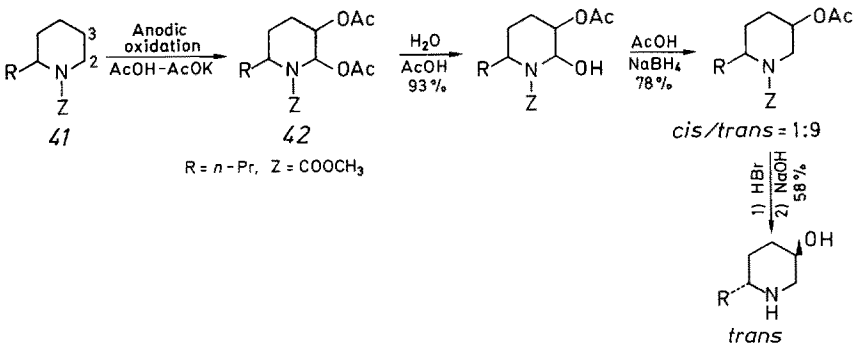
Piperidine skeletons are easily prepared by utilizing a unique [3 + 3]-type annelation between allyltrimethylsilane and α,α′-dimethoxylated amides which are easily



prepared either by anodic α-monomethoxylation of N-monoalkylamides followed by methoxylation of the α-methoxylated products or by anodic α,α′-dimethoxylation of N,N-dialkylamides [27]. The synthesis of a pharaoh ant trail pheromone *40* is shown below as a typical example.

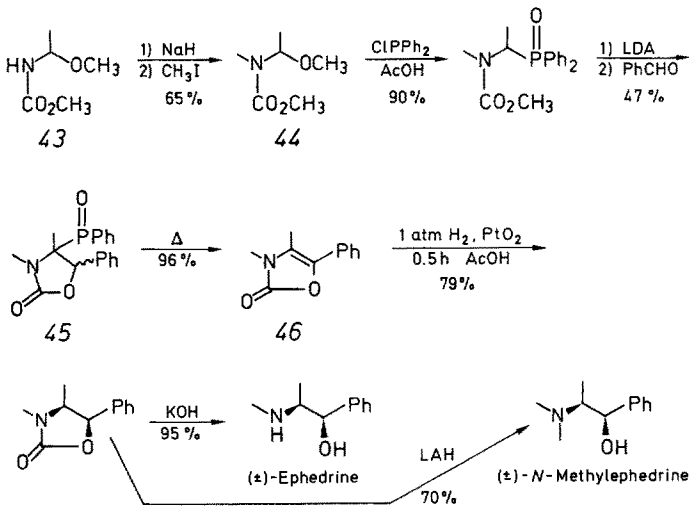
The annelation may proceed through the intermolecular allylation at the α-position of the α,α′-dimethoxylated starting material *39* followed by the intramolecular addition of the cation developed at the α′-position to the allylic double bond. The chlorine contained in the first product may come from the Lewis acid and is easily removable by catalytic hydrogenation.

Interestingly, the anodic oxidation of N-methoxycarbonylpiperidine derivatives *41* in AcOH affords 2,3-diacethoxylated products *42*. This reaction is conveniently applicable to the synthesis of Conium alkaloids such as pseudoconhydrine [28].



41 42 R = n-Pr, Z = $COOCH_3$

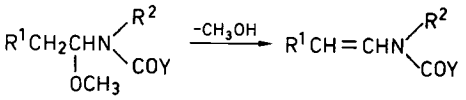
The synthesis of alkaloids described above is based on the generation of a cationic center at the position α to the nitrogen atom of an amide followed by a carbon-carbon bond formation at the α-position as the key reaction. On the other hand, developing an anionic center at the α-position of the N-acylamine generally requires a very strong base which may bring about undesirable side reactions. However, the formation of



43 44 45 46

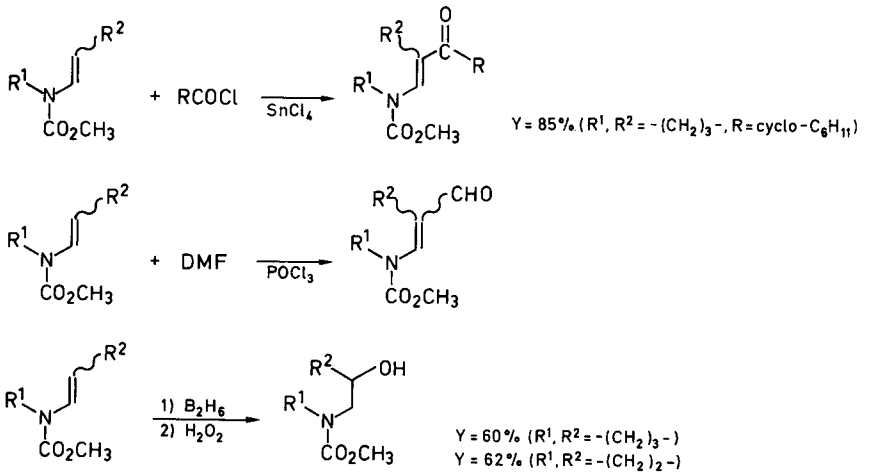
the α-anion of an N-acylamine *43* is easily achievable by the reaction of chlorodiphenylphosphine with α-methoxycarbamate *44* followed by deprotonation at the α-position. The product yielded by the reaction of the α-anion with an aldehyde easily forms the 2-oxazolidone ring *45*, which is one of the key points to make this synthesis stereoselective. The easy thermal removability of the diphenylphosphonyl group gives good access to the corresponding 2-oxazolone derivative *46* in high yield. The hydrogenation of the 2-oxazolone in acetic acid proceeds with perfect stereoselectivity. This method is successfully applicable to the synthesis of some physiologically active alkaloids having a vicinal erythro-aminoalcoholic moiety as exemplified by ephedrine [29].

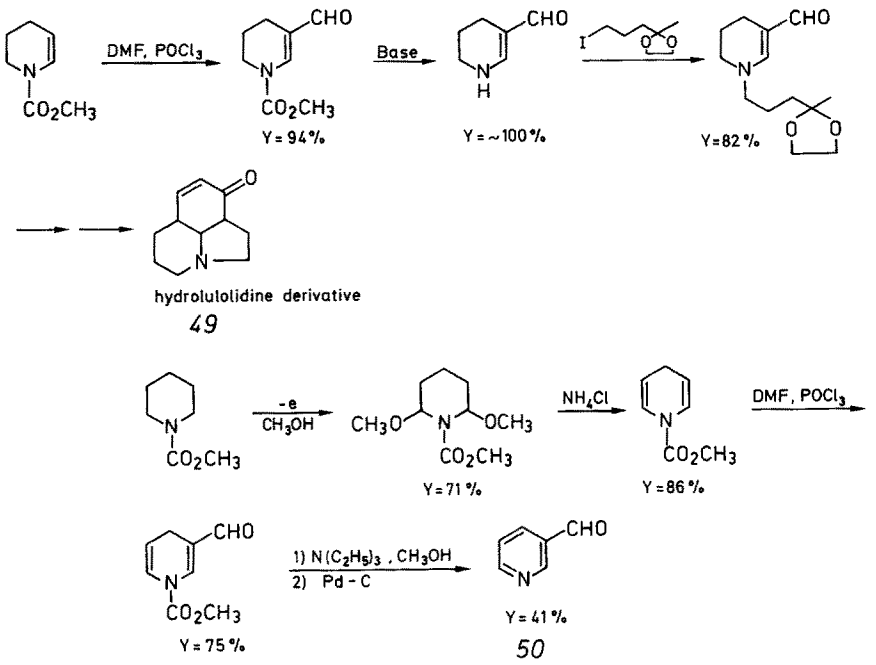
As described above, the carbon-carbon bond formation at the α-position of amines using anodically α-methoxylated carbamates as the starting compounds is highly useful for the synthesis of alkaloid type compounds, however, this method is limited only to the bond formation at the α-position. On the other hand, it has been found that the elimination of methanol from the α-methoxylated carbamates *47* yields the corresponding enecarbamates *48* in high yields [30].



47 *48*

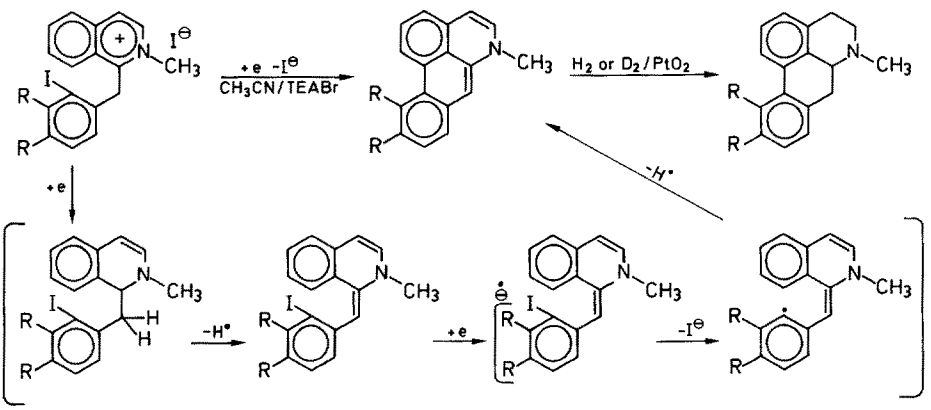
The formation of a carbon-carbon bond at the β-position of amines is made possible by the reaction of these enecarbamates with electrophiles. The acylation, Vilsmeyer reaction and hydroboration at the β-position of carbamates have been achieved by using this technique [31]. The syntheses of a derivative of hydrolulolidine *49* and nicotinaldehyde *50* are shown below as typical examples.





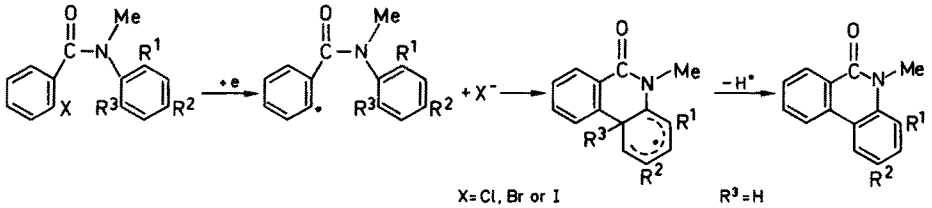
4 Reductive Addition and Substitution

The radical or anion species generated by electroreduction of halides are able to add to unsaturated systems such as aromatic ring and carbonyl group. The intramolecular addition of a radical species formed by electroreduction of an aromatic iodide to an aromatic ring has been applied to the synthesis of aporphines as it is shown in the following scheme [32].



The intermediary radical species is formed by an ECEC mechanism, and the first electroreduction takes place at the isoquinolinium moiety.

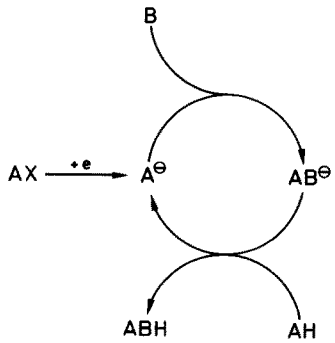
Electrochemical reduction of aromatic halides and subsequent intramolecular reaction of the resulting aromatic σ-radical with another aromatic ring have also been shown to be applicable to formation of a six membered hetero-ring containing nitrogen, though the products are not always directly related with natural alkaloids [33].



The formation of active carbanion species and their addition to electrophiles have also been observed in the cathodic reduction of carbon tetrachloride and trichloroacetic acid ester [34], though yields are not always satisfactory.

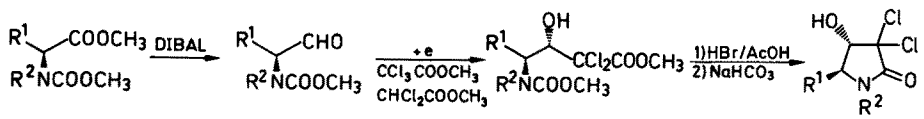
On the other hand, an electroreductively induced anionic chain reaction system has been found to be highly useful as a synthetic reaction [35]. In this reaction system, cathodic reduction of a halide AX forms an anion A^- in the first step, A^- attacks an electrophile B to yield an intermediate AB^-, and AB^- abstracts a proton from AH to regenerate the first anion A^-.

Therefore, if (a) AX is the only electrochemically reducible reagent in the reaction system, (b) the generated A^- reacts only with B, and (c) AH is more acidic than ABH, the reaction will proceed until the electrophiles are completely consumed and give the product ABH with high current efficiency.



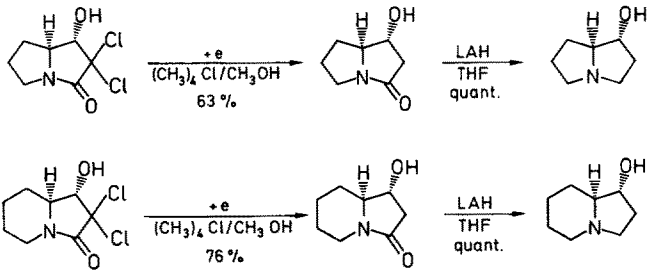
This type of chain reaction can be realized effectively by using carbon tetrachloride or trichloroacetic acid esters as AX, chloroform or dichloroacetic acid esters as AH, and aldehydes as B.

The optically active pyrrolizidine and indolizidine skeletons are stereoselectively synthesized by utilizing this chain reaction as one of the key reactions in which the

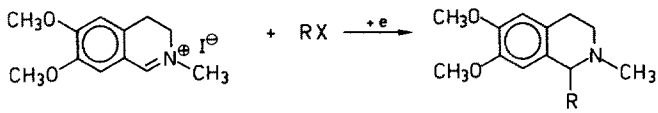


electrophile B is an α-amino aldehyde prepared from the corresponding α-amino acid [36].

The formation of the γ-lactams is almost perfectly diastereoselective if cyclic α-amino aldehydes or the aldehyde prepared from valine are used as starting materials. As it is shown in the following scheme, the electroreduction of the obtained optically pure γ-lactams followed by the reduction with LAH yields the corresponding optically pure pyrrolizidine and indolizidine skeletons.



Another methods for the electrochemical formation of the active carbanion is the cathodic reduction of iminium salts. When an iminium salt is reduced in the presence of a suitable alkylating agent, an alkyl group is introduced to the carbon atom of the imine. Some isoquinoline and indole type alkaloids are synthesized by using this substitution method as exemplified bellow by the synthesis of laudanosine *51* [37].

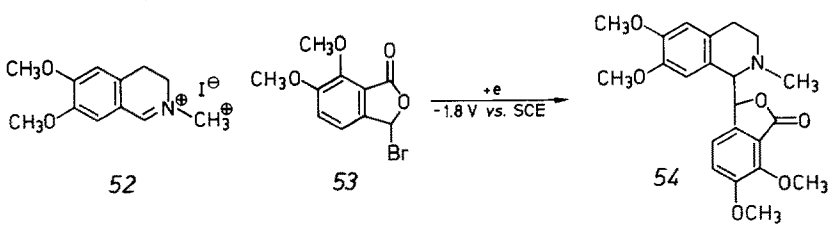


51

RX = $C_6H_5CH_2Br$ 65 %
RX = 4-CH_3O-$C_6H_4CH_2Br$ 73 %
RX = 3,4-di-CH_3O-$C_6H_3CH_2Br$ 85 %

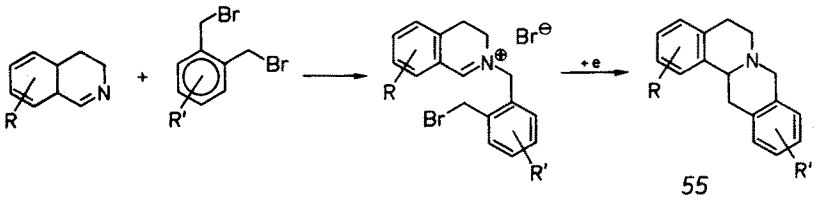
The reduction of the iminium salt to an anionic species has been suggested to be the initiation step, since the best yield is obtained when the working potential of the cathode has a value inbetween the reduction peak potential of the iminium salt and that of the alkylating agent.

This method is remarkably useful for the synthesis of some phthalide alkaloids which have been hitherto prepared by the Bishler-Napieralsky reaction. Condrastine I and II *54*, for instance, have been prepared from 2-methyl-3,4-dihydro-6,7-dimethoxy-isoquinolinium iodide *52* and 3-bromomeconine *53* in the total yield of 77% (ratio I:II = 42:35) [38].



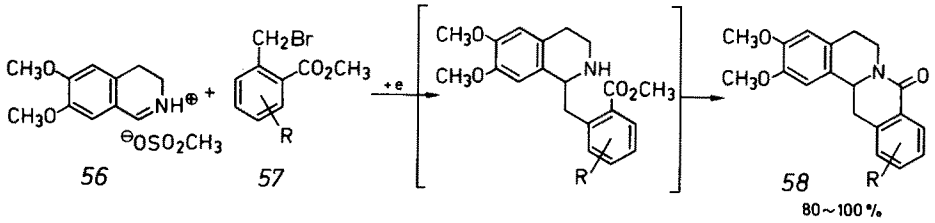
52 *53* *54*

This substitution method has been extended to an annelation reaction which is applicable to the synthesis of berbine (berberine) type alkaloids *55*.

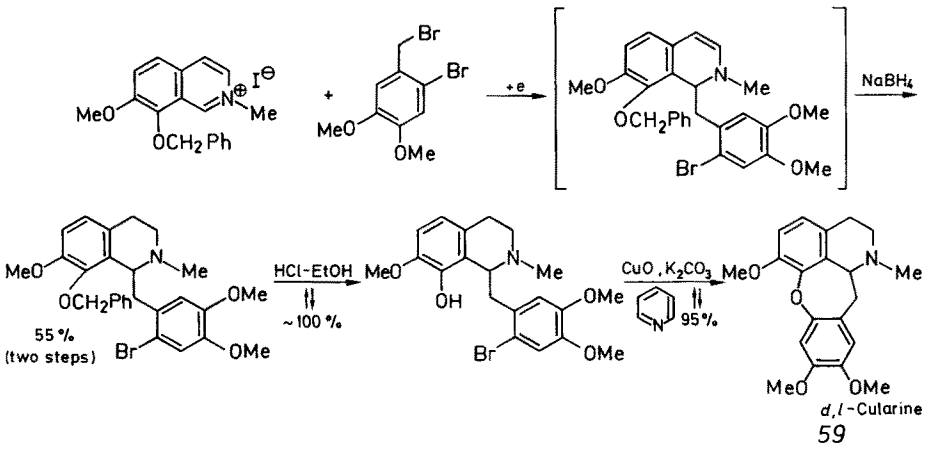


55

Although this method is simple, it is disadvantageous with respect to the following two points. First, the iminium salts prepared from imines and α,α'-dibromo-o-xylene in principle are mixtures of isomers, if two bromomethyl groups on α,α'-dibromo-o-xylene are made regionally unequal by the presence of substituents on their nucleus. Secondly, yields of the annelation are not always satisfactory. The formation of isomers can be avoided by the introduction of o-bromomethylbenzoates *57* as the electrophilic coupling component. As shown in the scheme below, the electroreduction of mixtures of iminium salts *56* and methyl o-bromomethylbenzoates *57* affords cyclized amides in high yields without forming isomers [39]. The reaction proceeds through reduction of iminium salts to anionic species followed by the attack of the anions on the bromomethyl group of the methyl o-bromomethyl esters and subsequent intramolecular aminolysis of amino esters yielding δ-lactams. Compounds of structure *55* are then easily obtained by reduction of *58*.



56 *57* *58* 80~100 %



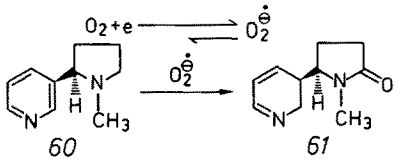
55 % (two steps) ~100 % 95 %

59

In the reaction of the electroreductively generated anion with substituted benzyl bromides, a bromine atom on the aromatic nucleus of the benzyl bromide is completely inert. This method has been used in the synthesis of cularine *59* [40].

5 Miscellaneous Reaction

Although cotinine is one of the important tobacco alkaloids and is known as the first metabolite of nicotine in the human body, the conventional chemical methods for its synthesis from nicotine are not always satisfactory. On the other hand, the oxygenation of nicotine *60* to cotinine *61* by using the electroreductively generated superoxide anion has been studied, since it has been mentioned that the anion may have a similar reactivity to the biological oxidation [41]. The maximum yield (65.2%) was obtained when the electroreduction was carried out at −0.9 V in aerating DMF with a carbon rod anode.



60 *61*

6 References

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Role of the Electrochemical Method in the Transformation of *beta*-Lactam Antibiotics and Terpenoids

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This review deals with the recent advances of the electrochemical methods a tools for the functionalization of beta-lactams and terpenoids. In the electrosynthetic conversions of beta-lactams, a regioselective functionalization of the appropriate hetero atom of the complex molecules without affecting other labile functional groups is a key operation. For this purpose, a novel electrochemical methodology which may involve the design of reaction sites in electrolysis media, new mediatory systems, two-phase electrolysis, and so on is recently developed. For the terpenoid syntheses, electro-generated recyclable mediatory reagents and superefficient catalysts utilized in the key stage of the conversions are highlights of this article.

1 Introduction

Organic synthesis of enantiomerically pure compounds starting from readily available biomolecules, which recently has been attracting much attention of synthetic chemists, allows direct access to stereochemically highly complex target molecules [1]. Besides the naturally occurring chiral biomolecules (biomass), e.g., terpenoids, amino acids, and carbohydrates, fermentation products have been proven particularly useful for chiral synthesis. This review deals with today's potentiality of electrochemical methods for the transformation of biomass, mainly focusing on the electrochemical transformation of *beta*-lactams and terpenoids.

In the electrosynthetic conversion of *beta*-lactams we face the problem of controlling redox reactions of hetero atoms, e.g., sulfur, nitrogen, halogens, etc. Probably, however, the solution to aspire to should allow a regioselective functionalization of the appropriate hetero atom of the complex molecules without affecting other labile functional groups. For such reasons, a novel electrochemical methodology is required which may involve the design of reaction sites in electrolysis media, such as new mediatory systems, two-phase electrolysis, and others [2]. For example, the penicillin-cephalosporin conversion by an ene-type chlorination, the selective oxidation of divalent sulfur and amino groups, the protection-deprotection of ester moieties, etc., have been performed by the two-phase electrolysis procedure and/or the proper choice of mediators [3]. For terpenoid conversion, electrogenerated recycable mediatory reagents and super-efficient catalysts are now being used [2a].

In this review, recent advances of electrochemical methods for the functionalization of *beta*-lactams and terpenoids will be focused upon.

2 Conversion and Functionalization of *beta*-Lactam Antibiotics

2.1 Electrochemical Ene-Type Chlorination

2.1.1 Penicillin-Cephalosporin Conversion via Thiazoline-Azetidinones

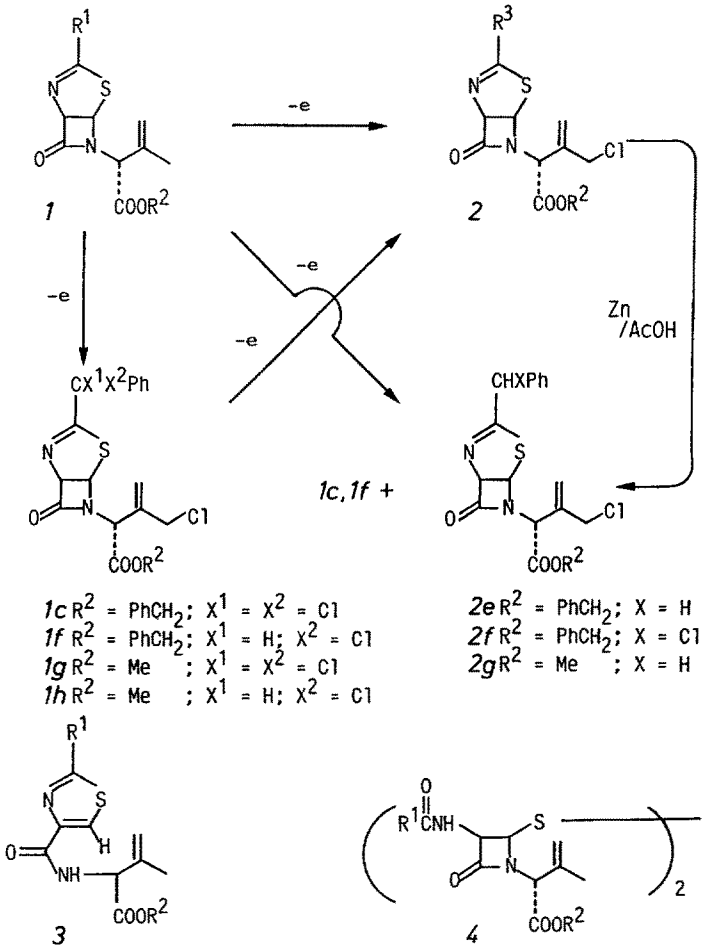
Thiazoline-azetidinones *1* derived from penicillins G and V [4] are potential intermediates for penicillin-cephalosporin conversion, where the oxidative functionalization of the methyl group of the 3-methyl-3-butenoate moiety is an essential step. The direct chlorination of *1* with chlorine (25 °C, 3 days) or *t*-butyl hypochlorite (—60% yields) gives the corresponding chlorinated compounds *2*, bearing benzyl, phenyl, *p*-tolyl, and phenoxymethyl groups as the R^3 substituents [5].

Chemoselective electrochlorination of the methyl group on the 3-methyl-3-butenoate moiety of thiazoline-azetidinone derivatives *1* has been performed in a CH_2Cl_2-aqueous H_2SO_4—(Pt or C) two-phase system [6]. The electrolysis of *1* (R^1 = $PhCH_2$, $PhCCl_2$, $PhOCH_2$, and PhC=O) provides chlorination products *1g* (R^1 = $PhCCl_2$), *2a*, *2b*, or *2f*, depending on the amount of electricity passed as well as on the concentration of Cl^- in the media (Scheme 2-1, Table 2.1). The trichlorination of *1a* (R^1 = $PhCH_2$, R^2 = Me) has been performed in an H_2O—CH_2Cl_2—$NaCl/H_2SO_4$—(Pt) system in an undivided cell at a constant current (10 mA/cm^2, 15 F/mol) at room temperature (entry 1). Carbon electrodes are used without any disadvantage (entry 2).

Table 2.1 Electrochlorination of Thiazoline-Azetidinones [6]

Entry	Substrate *1*			Electrolysis system	Electricity F/mol	Product *2* R^3 (Yield. %)	
		R^1	R^2				
1	*1a*	$PhCH_2$	Me	H_2O/CH_2Cl_2—(Pt)	15	*2a* $PhCCl_2$	(89)
2	*1a*	$PhCH_2$	Me	H_2O/CH_2Cl_2—(C)	15	*2a* $PhCCl_2$	(82)
3	*1b*	$PhCH_2$	$PhCH_2$	$H_2O/CHCl_3$—(Pt)	25	*2b* $PhCCl_2$	(76)
4	*1c*	$PhCCl_2$	$PhCH_2$	$H_2O/CHCl_3$—(Pt)	10	*2b* $PhCCl_2$	(85)
5	*1d*	$PhOCH_2$	Me	H_2O/CH_2Cl_2—(Pt)	10	*2c* $PhOCH_2$	(77)
6	*1e*	PhCO	Me	H_2O/CH_2Cl_2—(Pt)	5	*2d* PhCO	(80)

The effect of sulfuric acid is remarkable, since the absence of sulfuric acid results in a mixture of benzylic chlorides *1g* (25%), *1h* (20%), and the starting material *1a* (34%) together with complex compounds (20%). Notably, the two-phase electrolysis procedure brings about no hydrolysis products on either the thiazoline or the *beta*-

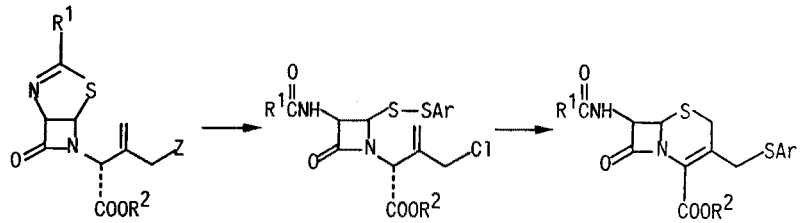


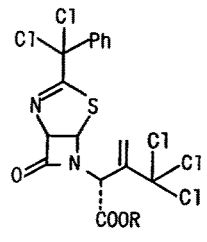
Scheme 2-1

lactam ring. In place of CH_2Cl_2, other hydrophobic solvents, e.g., $CHCl_3$ and AcOEt, can be used. The use of hydrophilic solvents, e.g., THF, CH_3CN, CH_3CN/THF, or CH_2Cl_2/THF, even in a two-phase system, facilitates hydrolysis of the thiazoline and/or the *beta*-lactam ring, leading to the ring-opened products *3* and/or *4*.

In the course of electrochlorination of *1b* (R^1 = $PhCH_2$) at a higher concentration of sodium chloride (1 g/3 ml) in water (entry 3), *gem*-dichloride *1c* (89%) is produced as an initial product when 10 F/mol of electricity is passed (Scheme 2-1). Electrolysis of the dichloride *1c* in the same medium gives *2b* in 85% yield (entry 4). The change of the product distribution is ascribed to the fact that the discharge of Cl^- at the anode may provide different chlorination agents, e.g., Cl_2, HOCl, Cl_2O, etc., depending upon the Cl^- concentration, the pH value of the media, oxidation potentials, and the nature of the aprotic solvents [7]. As shown in Fig. 2.1, the discharge of chloride ion at the anode produces the chlorine molecule, whose hydrolysis in an aqueous layer gives hypochloric acid when the medium is keeping the pH value weakly acidic and the concentration of chloride ion is less than 100 mg/3 ml. It is known that hypochloric acid is in equilibrium with chlorine oxide (Cl_2O) [7]. Chlorine and chlorine oxide would then migrate into the organic layer and react with olefins to give ene-type chlorination products. The conversion of *2a* and *2b* (R^3 = $PhCCl_2$) into the corresponding allylic chlorides *2e* and *2g* (R^3 = $PhCH_2$) is achieved in over 90% yields by removal of the benzylic chlorine atoms by zinc dust reduction in an $AcOH/CH_2Cl_2$ (1/4) system [6].

Most of the clinically significant cephalosporin antibiotics possess a sulfenyl group at the C-3′ position. The electrolytic ene-type chlorination products *2* are potent intermediates for the synthesis of 3′-substituted cephalosporins *6* (Scheme 2-2) [8].





Scheme 2-2

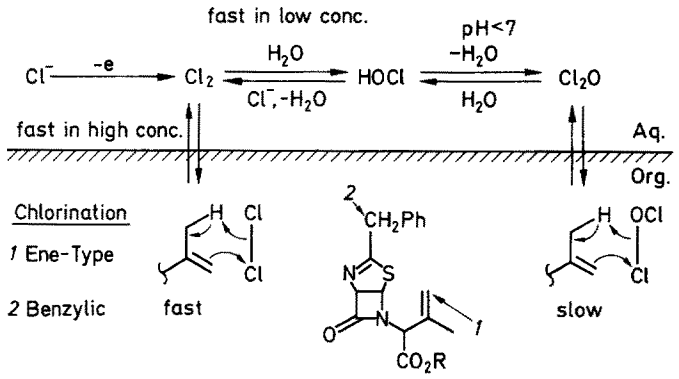


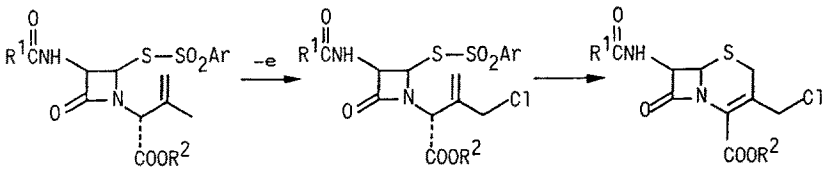
Fig. 2.1

Direct transformation of thiazoline-azetidinones *2* into 3′-thio-substituted cephalosporins *6* has been performed by ring opening of the thiazoline moiety with sulfenyl chloride followed by ring closure with ammonia in dimethylformamide and simultaneous displacement of the allylic chlorine atom with the leaving thiolates.

Photo-induced electrochlorination of thiazoline-azetidinone homologs *1* tends to give the pentachlorides *7*. The chlorination in an $H_2O/CHCl_3$—$NaCl/H_2SO_4$—(Pt) two layer system first gives the trichloride *2* (R^3 = $PhCCl_2$) in 80% yield after passage of 15 F/mol of electricity. Without isolation, the prolonged electrolysis under irradiation with a 750-W halogen lamp yields the pentachloride *7* in 50% overall yield. The conversion of *2* to *7* also proceeds under illumination in chloroform in the presence of chlorine to give *7* in 90% yield. The compounds *7* can be used for the synthesis of C-2 substituted cephalosporins [9].

2.1.2 Synthesis of 3-Chloromethyl-*delta*^{3}-cephems

Another application of the electrolytic ene-type chlorination is a straightforward synthesis of 3-chloromethyl-*delta*^{3}-cephems *10* from azetidinone *8* derived from natural penicillins [10]. 3-Chloromethyl-*delta*^{3}-cephems are known as important precursors in the synthesis of 3′-substituted cephalosporin antibiotics. They have been prepared by displacement of the acetoxyl group of 3-acetoxymethylcephalosporins with a chlorine atom [11]. The conversion of *8* to *10* comprises the electrolytic ene-type chlorination [12] of *8* and the ring closure of *9* with base (Scheme 2-3). Apparently, the arenesulfonyl



Scheme 2-3

groups ($Ar-SO_2$) have the property of both protecting the thiol groups at the C-4 position under the electrolysis conditions (*8* → *9*) and playing the part of leaving groups under the cyclization conditions (*9* → *10*). The ring closure of *9a* is performed

in a dry NH_3—DMF system at −20 to −30 °C to yield pure *10a* (R^1 = $PhCH_2$, R^2 = Me, 74%). Use of gaseous ammonia is shown to be most effective for the cyclization among the following bases (yields of *10a*): AcONa (29%), Et_3N (18%), KOH (17%), and KI (14%). Some results are summarized in Table 2.2.

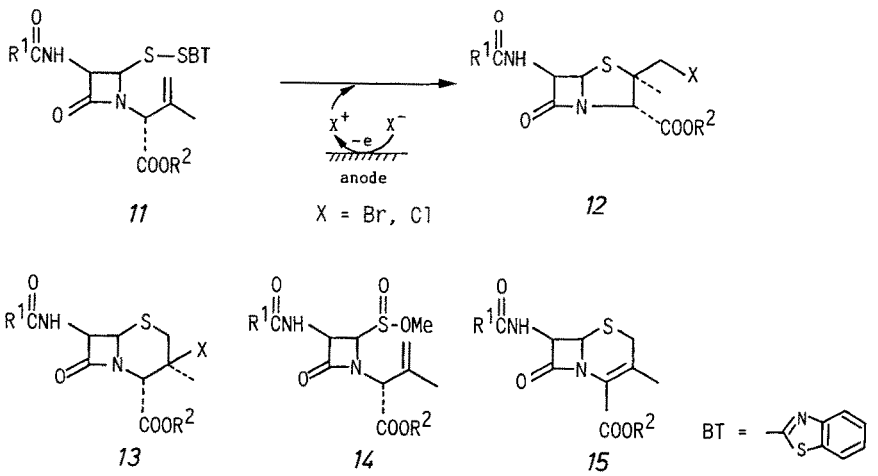
Table 2.2 Synthesis of 3-Chloromethyl-*delta*^{3}-cephems [12]

Entry	R^1	R^2	Ar^-	*8–9*	*9–10*
1	$PhCH_2$	Me	*p*-NO_2Ph	83	74
2	$PhCH_2$	Me	Ph	77	82
3	$PhCH_2$	$PhCH_2$	*p*-NO_2Ph	91	86
4	$PhCH_2$	$PhCH_2$	Ph	84	78
5	$PhCH_2$	*p*-NO_2PhCH_2	*p*-NO_2Ph	75	52
6	PhCO	$PhCH_2$	*p*-NO_2Ph	94	93

2.2 Electrooxidation of the Divalent Sulfur Atom

2.2.1 Sulfur-Sulfur Bond Cleavage of Kamiya's Disulfides

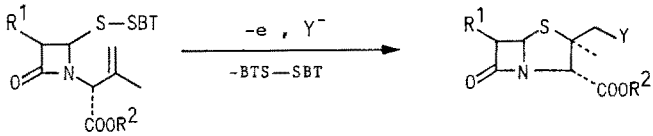
In connection with the penicillin-cephalosporin conversion, 4-(2-benzothiazolyldithio)azetidinones (Kamiya's disulfide) *11* derived from penicillins G and V are one of the most actively investigated intermediates. Namely, the disulfides *11* can be converted by the action of bromine or cupric chloride in methylene dichloride to the corresponding 2*beta*-halomethylpenicillins *12* (X = Br, Cl), precursors of cephalosporin antibiotics [13]. Alternatively, an electrooxidative sulfur-sulfur bond fission of Kamiya's disulfide *11* has been investigated by two groups under different electrolysis conditions, leading to either 2*beta*-halomethylpenicillins *12* and 3*beta*-halocephams *13*, or 4-methoxysulfinylazetidinone derivatives *14* (Scheme 2-4). Thus, the electro-



Scheme 2-4

lysis of the disulfides *11* in a MeCN/H_2O(trace)—Me_4NBr/$ClCH_2CO_2H$—(Pt) system exclusively yields 2*beta*-bromomethylpenams *12* (X = Br), which can lead to 3*beta*-bromocephams *13* (X = Br) (40–45%) together with *delta*^{3}-cephems *15* (4–6%) by column chromatography [14]. Independently, the electrooxidation of Kamiya's disulfides *11* has been performed under different conditions, leading to either *12*, *13*, or 4-(methoxysulfinyl)azetidinone derivatives *14*. Thus, the electrolyses of *11* in MeCN/THF/H_2O (6/1.5/0.3)-halide salt-(Pt/Pt) or CH_2Cl_2/H_2O (5/3)-halide salt-(Pt/Pt) systems give mainly *12* and *13*. Among various kinds of bromide salts, magnesium dibromide is the most effective one for this purpose. The use of alkaline metal salts, e.g., LiBr, NaBr, and KBr or HBr in place of $MgBr_2$, affords a mixture of *12* and *13* in 73–46% yields. The product ratio of halopenicillins *12* to halocepham *13* varies remarkably, depending on the choice of halide salts as well as the electrolysis conditions. For example, the ratio of *12* to *13* (X = Br) is affected by the temperature as follows: temperature, *12*/*13* (total yield): 23–25 °C, 54/46 (96%); 5–9 °C, 80/20 (100%); −3 to −5 °C, 88/12 (90%). The transformation of *12* into *13* (X = Br) can be performed by standing in *N*,*N*-dimethylformamide at room temperature overnight [2a] and subsequent chromatography on an alumina column to afford deacetoxycephalosporin *15* (R^1 = $PhCH_2$, R^2 = CH_3, 95%). The electrolysis of *11* in a MeOH—H_2SO_4—(Pt) system gives 4-(methoxysulfinyl)azetidinone *14* (R^1 = $PhCH_2$, R^2 = CH_3, 53%), a new class of intermediates for *beta*-lactam antibiotic synthesis [15].

The disulfide *16* can be converted to various 2*beta*-methyl-substituted penicillins *17* by electrochemical methods (Scheme 2-5) [16]. For example, the electrolysis of *16*



16 *17*

Scheme 2-5

(R^1 = H; R^2 = PNB) in a C_6H_6/H_2O/MeCN/AcOH(6:3:1:1)—KSeCN—(Pt) system at a current density of 7 mA/cm^2 yields methyl 2*beta*-cyanoselenomethylpenicillin *17* (Y = SeCN) in 90% yield. Similarly, thiocyano and azide groups can be introduced at the C-2 *beta* position of penams; the representative electrolysis conditions are shown in Table 2.3.

Table 2.3 Electrosynthesis of 2*beta*-Substituted Methylpenicillins [16]

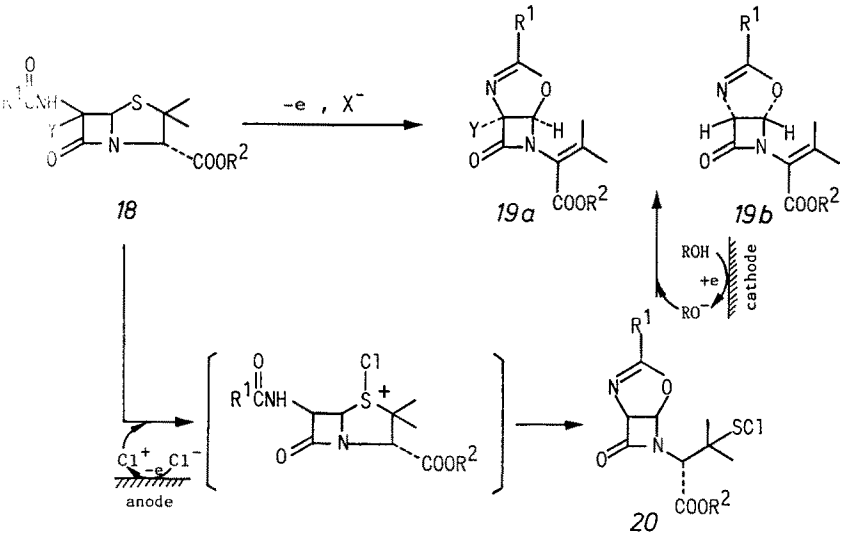
Entry	Disulfide *16*[a]			Conditions	F/mol	Product *17* Yield (%)
	R^1	R^2	Y^-			
1	H	PNB	KSeCN	C_6H_6/MeCN/H_2O—AcOH	22	90
2	H	PMB	KSCN	CH_2Cl_2/H_2O—H_2SO_4	14	98
3	Br	PNB	KSCN	CH_2Cl_2/H_2O—H_2SO_4	14	54
4	G	Bn	KSCN	CH_2Cl_2/H_2O—H_2SO_4	27	80
5	H	PNB	NaN_3	DMF—AcOH	6	50

[a] PNB: *p*-nitrobenzyl; PMB: *p*-methoxybenzyl; Bn: benzyl; G: $PhCH_2CONH$

2.2.2 Direct Transformation of Penicillins into Oxazoline-Azetidinones

The sulfur-free analogs of penicillins and cephalosporins have attracted much attention of both synthetic and medicinal chemists, since the successful development of new 1-oxacepham antibiotics by the Shionogi group [17]. Namely, oxazoline-azetidinone derivatives *19* have been used as key intermediates in the synthetic chemistry of new *beta*-lactam antibiotics [18]. The compounds *19* have usually been prepared by a two-step operation involving the reaction of *19* with chlorine or *t*-butylhypochlorite followed by treatment with a base.

The direct conversion of penicillins *18* into the oxazolines *19* is performed by the halide salt-mediated electrolysis in an undivided cell (Scheme 2-6). The electrolysis con-



Scheme 2-6

Table 2.4 Direct Transformation of Penicillins into Oxazoline-Azetidinones [19]

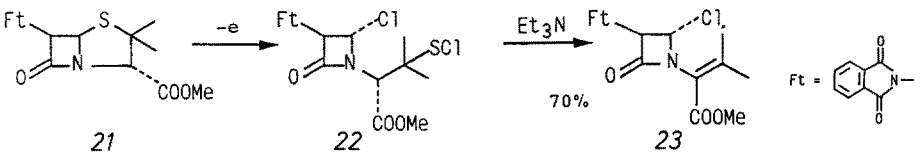
Entry		Penicillin			Electrolysis system[a]	Temp. °C	Electricity F/mol	Product (Yield, %)
		Y	R^1	R^2				
1	*18a*	α-H	$PhCH_2$	Me	A	−70	3	*19a* (82)
2	*18a*	α-H	$PhCH_2$	Me	A	−40	3	*19a* (45)
3	*18a*	α-H	$PhCH_2$	Me	A	0	3	*19a* (20)
4	*18a*	α-H	$PhCH_2$	Me	B	−40	5	*19a* (81)
5	*18a*	α-H	$PhCH_2$	$PhCH_2$	B	−40	5	*19a* (65)
6	*18a*	α-H	$PhOCH_2$	Me	B	−40	5	*19a* (74)
7	*18a*	α-H	Ph	Me	B	−40	5	*19a* (72)
8	*18a*	α-H	Ph	Ph_2CH	B	−40	5	*19a* (93)
9	*18c*	α-OCH_3	$PhCH_2$	Me	C	0	5	*19c* (71)
10	*18b*	β-H	$PhCH_2$	Me	B	−40	6	*19b* (80)

[a] A: LiCl (0.19 mmol)-methanol (2 ml)-*t*-butyl alcohol (0.5 ml); B: $MgCl_2$ (2 ml)-methanol (2.5 ml)-*t*-butyl alcohol (0.5 ml); C: $MgCl_2$ (0.1 mmol)-methanol (2 ml)-tetrahydrofuran (0.5 ml)

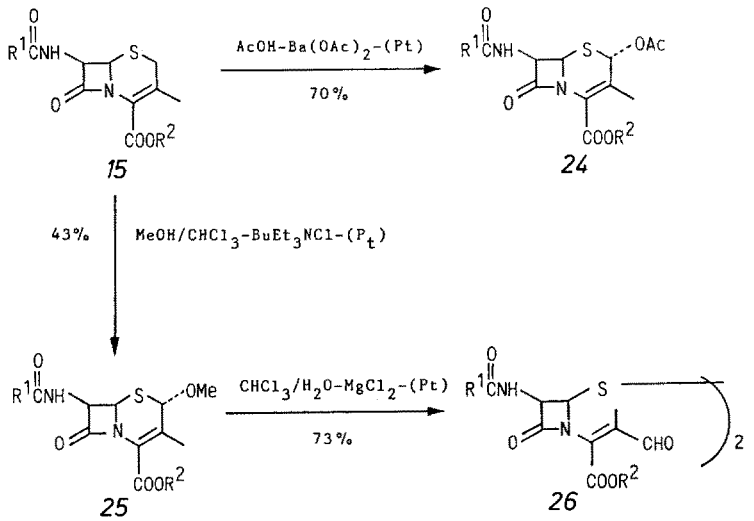
ditions and results are summarized in Table 2.4 [19]. The temperature (—70 °C) is critical (entry 1), since the electrolysis at —40 to 0 °C brings about a considerable amount of the beta-lactam ring-opening products, affording only 45 — 20% of *19a* (entries 2 and 3). In contrast, use of magnesium dichloride in place of lithium chloride provides good results even at —40 °C, affording *19a* in 81% yield (entry 4). The electrolysis of penicillins *18* in a MeOH—$MgCl_2$ system at —40 °C yields the oxazolines *19a* smoothly (entires 5–9). 6-Epi-penicillin *18* (Y = beta-H; R^1 = $PhCH_2$; R^2 = CH_3) affords epi-oxazoline-azetidinone *19b* (R^1 = $PhCH_2$; R^2 = CH_3) in 80% yield (entry 10).

The transformation of *18* into *19* proceeds as follows: the C-5 S bond cleavage is promoted by attack of the electrogenerated $[Cl]^+$ (or Cl_2) and the subsequent replacement by the C-6 amide oxygen gives the oxazoline-azetidinones *20* which, in turn, suffer desulfurization by a EG base (CH_3O^- or *t*-BuO^-) (a paired reaction, Scheme 2-6). The oxazoline-azetidinone *20* can be isolated when the electrolysis is carried out in an acidic medium. Namely, the electrolysis of *18* (Y = *alpha*-H; R^1 = $PhCH_2$; R^2 = CH_3, 0.31 mmol) in a $CHCl_3/H_2O$—HCl/$PhCH_2Me_3NCl$—(Pt) system at 0 °C affords *20* (R^1 = $PhCH_2$; R^2 = CH_3). Treatment of *20* with a THF—MeOLi system at —70 °C gives *19* (Y = H; R^1 = $PhCH_2$; R^2 = CH_3) in 60% yield from *20*.

6-Phthalimidopenicillin *21*, which is not able to produce the oxazoline system, affords azetidinone *22* upon electrolysis in acidic media, and subsequent treatment of *22* with triethylamine gives the chlorinated azetidinone *23* in 70% overall yield (from *21*, Scheme 2-7) [19].



Scheme 2-7



Scheme 2-8

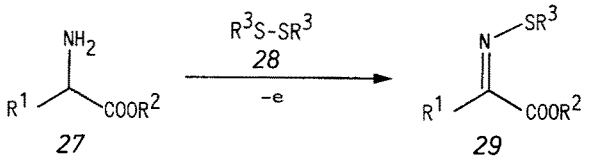
2.2.3 Functionalization of Cephalosporins at the C-2 Position

Several synthetic procedures for the preparation of C-2-acetoxy- and methoxy-cephalosporins have been reported [20]. The functionalization at the C-2 position of cephalosporin *15* can be started with the oxidation of the divalent sulfur atom which produces sulfenium cation intermediates, which are precursors of C-2-substituted cephalosporins. The electrochemical conversion of cephalosporins *15* into their C-2-substituted homologs has been realized [21]. For example, the electrochemical acetoxylation at the C-2 position of desacetoxycephalosporin *15* is carried out in an AcOH—$Ba(OAc)_2$—(Pt) system to give the C-2-acetoxylated products *24* (R^1 = CH_2OPh; R^2 = Me) in 70% yield (Scheme 2-8). Electromethoxylation at the C-2 position of *15* is performed in a $MeOH/CHCl_3$—$BuEt_3NCl$—(Pt) system to give the compounds *25* (R^1 = CH_2OPh; R^2 = CH_2Ph) in 43% yield. The methoxylated product *25* can lead to the further oxidized product *26* by electrolysis in a $H_2O/CHCl_3$—$MgCl_2$—(Pt) two-layer system.

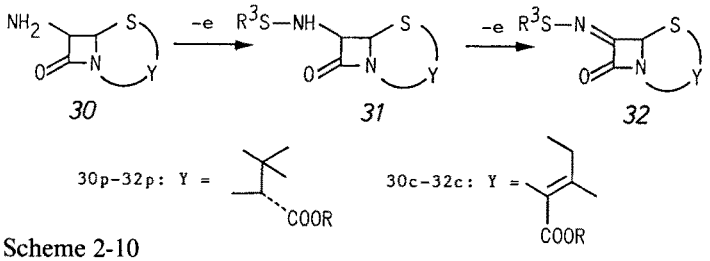
2.3 Electrooxidation of Amine and Amide Functions

2.3.1 Functionalization of Penicillins and Cephalosporins at the C-6 and C-7 Positions

Direct transformation of *alpha*-aminoalkanoates *27* to the corresponding sulfenimines *29* by electrolysis with disulfide *28* in a CH_2Cl_2/H_2O—$MgBr_2$—(Pt) system has been developed (Scheme 2-9) [22]. The procedure can be applied to the sulfenylation of C-6/C-7 amino groups of penicillins and cephalosporins *30* (Scheme 2-10).



Scheme 2-9

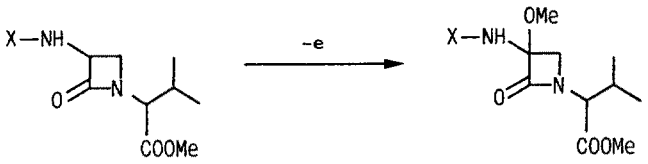


Scheme 2-10

The two-phase electrolysis system (H_2O/CH_2Cl_2) is effective for the successful transformation of *30* and disulfide *28* into *32*. For example, electrolysis of *30p* and the disulfide *28* (R^3 = Ph) in a $CH_2Cl_2/MeOH/H_2O$ (10/2.5/10)—$MgBr_2$—(Pt) system affords 72% yield of sulfenimine *32p* (R^3 = Ph). In a similar manner, sulfenimines *32p* (R^3 = BT, 72%) and *32c* (R^3 = Ph, 60%) are synthesized. Interestingly, the intermediary sulfenamide *31p* (R^3 = BT) has been isolated in 87% yield by interrupting the electrolysis after passage of 3 F/mol of electricity. Conversion of *31p* to *32p* can be performed under similar electrolysis conditions in 71% yield.

2.3.2 Methoxylation of *alpha*-Amino-*beta*-lactams

A synthetic method of introducing a methoxy group into the *alpha* position of *alpha*-amino acid derivatives and *alpha*-amino-*beta*-lactams has been exploited by employing an indirect electrooxidation process [23]. For example, the electrolysis of the lactam *33a* in a MeOH—NaCl—(Pt) system yields the methoxylated lactam *34a* in 92% yield. The indirect methoxylation of *beta*-lactams proceeds successfully without cleavage of the azetidinone ring (Scheme 2-11).



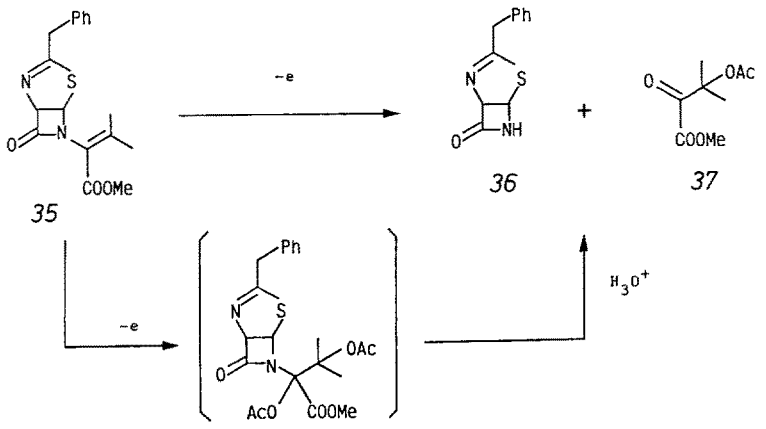
33a X = COOMe
33b X = $COOCH_2Ph$

34a 92% (4.3 F/mol)
34b 30% (4.0 F/mol)

Scheme 2-11

2.3.3 Elimination of *N*-Substituents of *beta*-Lactams

Thiazoline-azetidinone *36* is a versatile intermediate for the synthesis of varieties of *beta*-lactam antibiotics [24]. The most straightforward route to *36* must be the removal of the *beta*-lactam *N*-substituents of thiazoline-azetidinone *35*, which is readily obtained from penicillins by Copper's method [4]. This has usually been done by the two-step operation, involving ozonolysis and subsequent methanolysis [25]. Direct transformation of *35* to *36* also has been achieved by oxidation with potassium permanganate or osminum tetraoxide, but yields are unsatisfactory (—37%) [25]. An efficient method for the removal of *N*-substituents of *35* is the electrochemical acetoxylation procedure which may lead to the compound *36* along with *37* (Scheme 2-12) [3]. For example, the

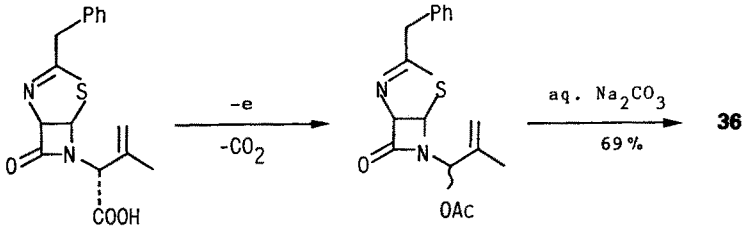


Scheme 2-12

electrolysis of *35* is carried out in a AcOH/EtOAc/Ac_2O—Et_3N—(Pt—Cu) system, affording *36* in 94% yield (60% conversion) together with the acetoxyester *37*. This

reaction first would undergo the electroacetoxylation of *35* to give intermediate *38* which is hydrolyzed either during the electrolysis or workup to afford *36*.

An alternative electrochemical route to the thiazoline-azetidinone *36* also has been developed. Carboxylic acid *39* prepared from penicillin G can be converted to *36* via *40* by electrochemical decarboxylative acetoxylation followed by hydrolysis (Scheme 2-13) [5]. The electrolysis of *39* in an AcOH/DME—AcONa—(C) system at 0 °C

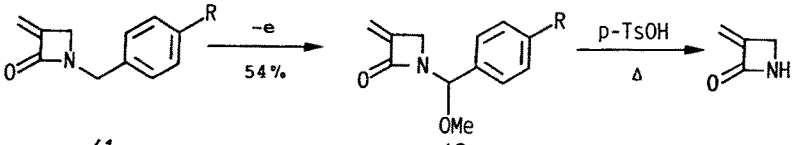


39 *40*

Scheme 2-13

yields the acetate *40* in 80% yield. Hydrolysis of *40* is achieved by adding aqueous sodium carbonate slowly to the methanol solution of *40*, affording *36* in 69% yield.

Debenzylation of *N*-benzyl-*beta*-lactams *41* has been achieved by electrooxidative methoxylation of *41* at the benzylic position followed by hydrolysis with *p*-toluenesulfonic acid in acetone [27]. For example, the electrolysis of *N*-benzyl-3-methylene-*beta*-lactam *41* (R = OMe) in an MeOH—Et_4NClO_4—(Pt) system in an undivided cell forms *N*-methoxybenzyl-3-methylene-*beta*-lactam *42* (R = MeO) in 54% yield (Scheme 2-14). The debenzylation of *42* is carried out on treatment with *p*-toluenesulfonic acid in aqueous acetone to give 3-methylene-*beta*-lactam *43* in 50% yield.



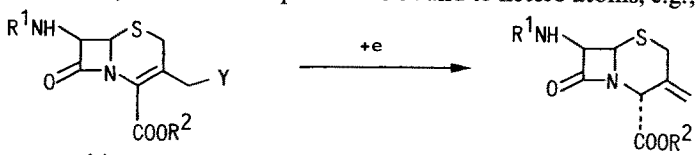
41 *42* *43*

Scheme 2-14

2.4 Electroreductive Removal of C-3′ and C-3 Substituents of Cephalosporins

2.4.1 Reductive Removal of C-3′ Substituents of Cephalosporins (Synthesis of 3-Methylenecephams)

3-Methylenecephams *45* are useful precursors of 3-norcephalosporins, unnatural *beta*-lactam antibiotics, where the C-3 position is bound to hetero atoms, e.g., chlorine



44 Y = OAc
10 Y = Cl
6 Y = SBT

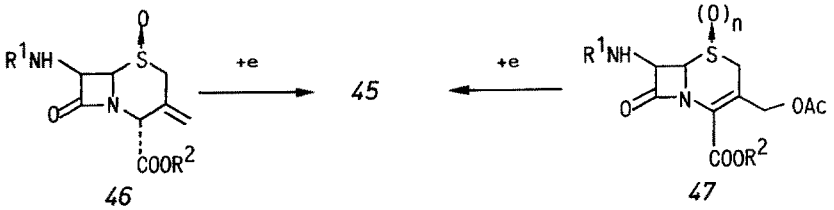
45

Scheme 2-15

or the methoxy group. 3'-Acetoxycephalosporin *44* is a suitable precursor for the preparation of 3-methylenecephams *45* (Scheme 2-15). Electroreductive preparation of 3-methylenecepham derivatives has been performed by Ochiai and coworkers in 1972 [28]. The electrolysis of 3'-acetoxycephalosporanic acid *44* in aqueous HCl—Na_2HPO_4 (0.1 *M*, pH 7)-(Pt/Hg) gives the corresponding 3-methylenecepham *45* in 81% yield. The electroreduction mechanism of cephalosporin derivatives has been investigated independently [29].

Another straightforward access to *45* is the electroreductive dechlorination of 3'-chlorocephalosporin *10* [30]. The electrolysis of *10* has been carried out in a THF/H_2O(4/1)—$LiClO_4/NH_4ClO_4$—(Pt/Pb) system in a divided cell to give *45* in 87% yield. Proper choice of the cathode material is important. Namely, a lead cathode is indispensable for the successful conversion of *10* to *45*, because the yield of *45* varies depending on the choice of cathode materials in the following order: Pb (87%), carbon (58%), Cu (51%), Pt (19%). In a similar manner, 3'-(2-benzothiazolylthio)-cephalosporin *6* (Ar: Benzothiazolyl) also can be converted into 3-methylenecepham *45* in 78–90% yields [30].

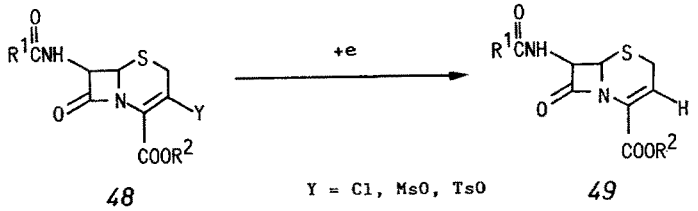
3-Methylenecepham *45* has also been synthesized by electroreduction of cephalosporin *S*-oxide *46* and *47* (Scheme 2-16) [31].



Scheme 2-16

2.4.2 Reductive Removal of C-3 Substituents of Cephalosporins

The cephalosporins bearing a hydrogen atom at C-3 position play an important role in antibiotics research. Electrochemical access from C-3-substituted cephems *48* has been developed. The reductive removal of the C-3 substituents of *48* (Y = Cl, MsO, TsO) has been carried out in a McIlvain buffer solution (pH 8–7) in the presence of tetrabutylammonium iodide to give the compounds *49* in good yields (Scheme 2-17) [32].



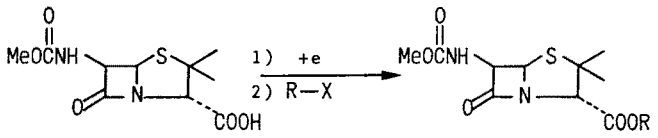
Scheme 2-17

2.5 Protection and Deprotection of Acids and Esters

2.5.1 Electrogenerated (EG) Base-Assisted Esterification of Penicillanic Acid

A mild and simple procedure for the esterification of penicillanic acids is an essential technique. The EG base derived from the electroreduction of 2-pyrrolidone has been

shown to promote the esterification of carboxylic acids [33]. The electrochemical esterification has been carried out in a DMF—R_4NBr—(Pt) system in the presence of 2-pyrrolidone by passing 2 F/mol of electricity. To this solution, a DMF solution of penicillanic acid *50* and benzylbromide is added and the usual workup gives the benzyl ester *51a* in 86% yield (Scheme 2-18).



50

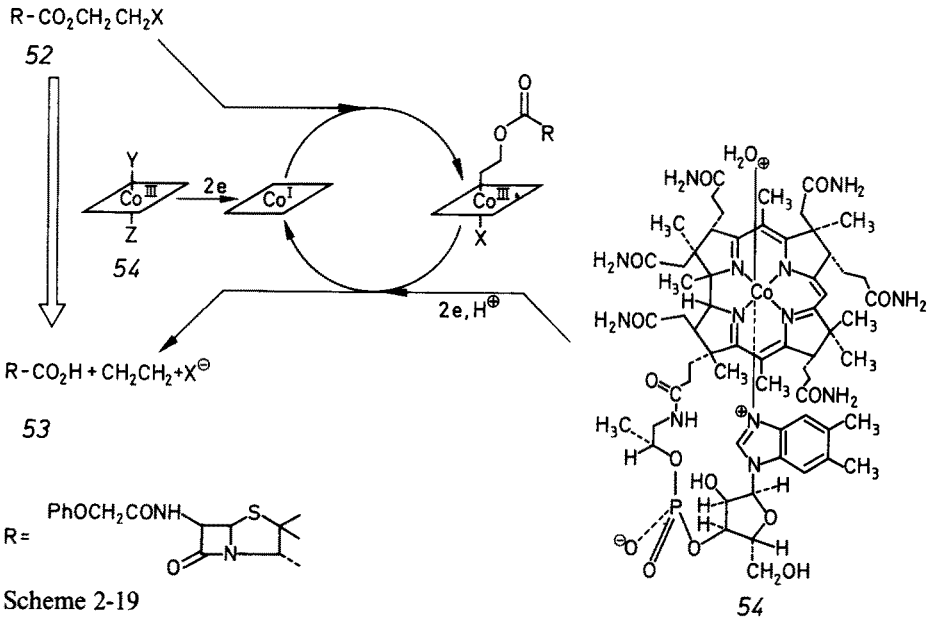
51a R = $C_6H_5CH_2$ (86%)

51b R = MeOCO-$C_6H_4CH_2$ (65%)

Scheme 2-18

2.5.2 Deprotection of Ester Groups of Penicillins and Cephalosporins

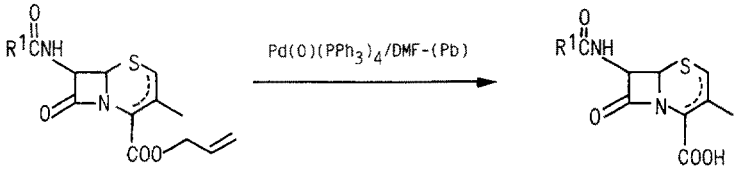
The electroreductive hydrolysis of ester groups of penams and cephams leading to the corresponding acids is an important technique due to the reason that the deprotection can be carried out under very mild and neutral conditions. The reductive removal of a *beta*-bromoethyl protecting group from the corresponding penicillin V ester *52* has been successfully carried out in an EtOH/H_2O(4/1)—$LiClO_4$/NH_4ClO_4—(Hg) system in the presence of aquocobalamine *54* as an electron transfer catalyst at —1.95 V (Ag/Ag^+) at 1 °C to yield the penicillanic acid *53* in 95% yield (Scheme 2-19) [34].



Scheme 2-19

The electroreduction procedure can also be used effectively for the deprotection of allyl esters. Palladium(0)catalyzed electroreductive cleavage of allylic esters has been performed in an MeCN—Et_4NOTs—(Pt/Pb) system in the presence of Pd(0)—

$(PPh_3)_4$ as an electron transfer catalyst (Scheme 2-20) [35]. Thus, the electroreductive removal of the allyl group from cephalosporin allyl esters *55* yields the corresponding acids *56* in 72% yield.



55 *56*

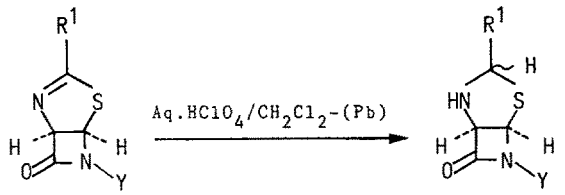
Scheme 2-20

The direct electroreductive conversion of cephalosporin *p*-nitrobenzyl esters into their corresponding acids has been carried out in a DMF-10% H_2SO_4—(Hg) system [36].

2.6 Miscellaneous Functionalization

2.6.1 Hydrogenation of Thiazoline-Azetidinones

Tiazolidine-azetidinones *58* are useful intermediates for cephalosporin antibiotic synthesis. The hydrogenation of thiazoline-azetidinones *57* prepared from penicillins G and V must be a straightforward route leading to *58*. The electro-hydrogenation of the C=N double bond of *57* in an aqueous CH_2Cl_2—$HClO_4$—(Pt) system by changing the current direction every 30s gives *58* in 77–100% yields (Scheme 2-21) [37].

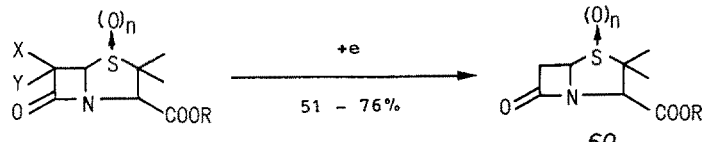


57 *58*

Scheme 2-21

2.6.2 Reductive Dehalogenation of 6,6-Dihalo- and 6-Halo-penicillins

C-6-Nonsubstituted penicillin derivatives have received considerable attention as a new *beta*-lactamase inhibitor. In this connection, reductive removal of the halogen atoms attached to the *alpha*-carbon atom of the *beta*-lactam ring has been performed. Electroreduction of bromo- and chloro-penicillins *59* (n = 0–2) in DMF/AcOH/

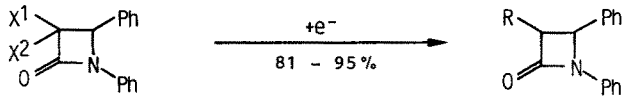


59 X = Br, Cl
Y = Br, H

60

Scheme 2-22

$MeOH/Et_4NClO_4$ gives the corresponding C-6-nonsubstituted penicillins *60* in 51–76% yields (Scheme 2-22), respectively [38]. Reductive dehalogenation of 3-bromo and 3-chloroazetidinone *61* is carried out in various electrolysis media (Scheme 2-23).



61

X^1 = Cl, Br
X^2 = H, Cl

62

a R = H
b R = CO_2H
c R = CH_3CO

Scheme 2-23

For example, electroreduction of *61* in DMF/Et_4NClO_4 containing acetic acid as a proton source gives the hydrogenation product *62a* (98–100%) while electroreduction of *61* in CO_2-saturated media affords carboxylic acid *62b* (81–95%) [39]. Acetylation at the *alpha*-carbon atom is also achieved by the electroreduction of *61* in the presence of a 10-fold excess of acetic anhydride (30–70%) [40].

2.6.3 Other Reactions

Reductive cyclization of *alpha*-bromoacetamides and 3-bromopropanamide to *beta*-lactams has been performed by electroreduction in the presence or absence of a probase [41]. The cyclization seems to involve the reductive cleavage of carbon-halogen bonds generating carbanions which would act as nucleophiles or bases in the electrolysis media.

N-alkylation of azetidinone with electrogenerated base in DMF/Et_4NOTs containing pyrrolidinone as a probase has been reported. *N*-Methyl- and butyl-azetidinones are prepared in good yields by this procedure [42].

3 Conversion and Functionalization of Terpenoids

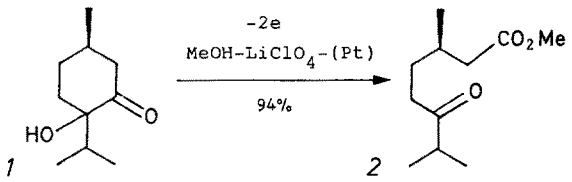
Recently there has been a marked progress of electroorganic chemistry in the field of electrochemical transformations of naturally occurring biomolecules [43]. Inevitably, the recent matter of concern is directed towards the elucidation of the synthetic potentiality of electroorganic reactions to specific groups of biomolecules. The following is intended to clarify the role of electrochemistry in the terpenoid field.

3.1 Carbon-Carbon Bond Cleavages

3.1.1 Oxidative Cleavage of Carbon-Carbon Bonds of Terpenoids

Oxidative C—C bond cleavage of vicinally oxygenated alicyclic terpenoids is the method of choice to prepare oxoalkanoates and alkanediones, giving access to chiral synthetic building blocks. Electrochemical carbon-carbon bond cleavage reactions have been investigated on 1,2-diols [44, 59], 2-amino-1-ols [45, 46], and 1,2-diamines [46]. Recently, the electrooxidative cleavage of 2-oxo- [47, 48], and 2-phenylthio-1-cyclo-

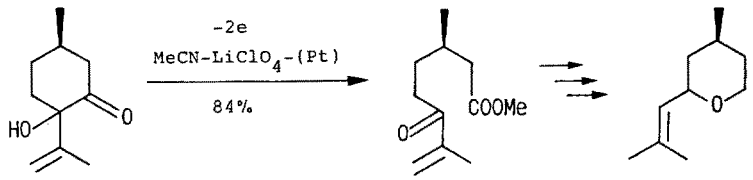
alkanols [49], cycloalkanone enol acetates [48] or enol ethers [50], and *alpha,beta*-epoxycycloalkanones [51], leading to the corresponding oxoalkanoates or alkanediones has also been performed. The electrolysis of (+)-4-hydroxy-*p*-menth-3-one *1* in an MeOH—$LiClO_4$—(Pt) system at an applied voltage of 20 V affords methyl (—)-6-oxo-6,7-dihydrocitronellate *2* in 94% yield (Scheme 3-1) [48]. This procedure can be



1 *2*

Scheme 3-1

successfully applied to a (+)-rose oxide *5* synthesis. The desired chiral intermediate *4* can be obtained in 84% yield by electrolysis of *3* in an MeOH—$LiClO_4$—(Pt) system at 8–10 °C (Scheme 3-2).



3 *4* *5*

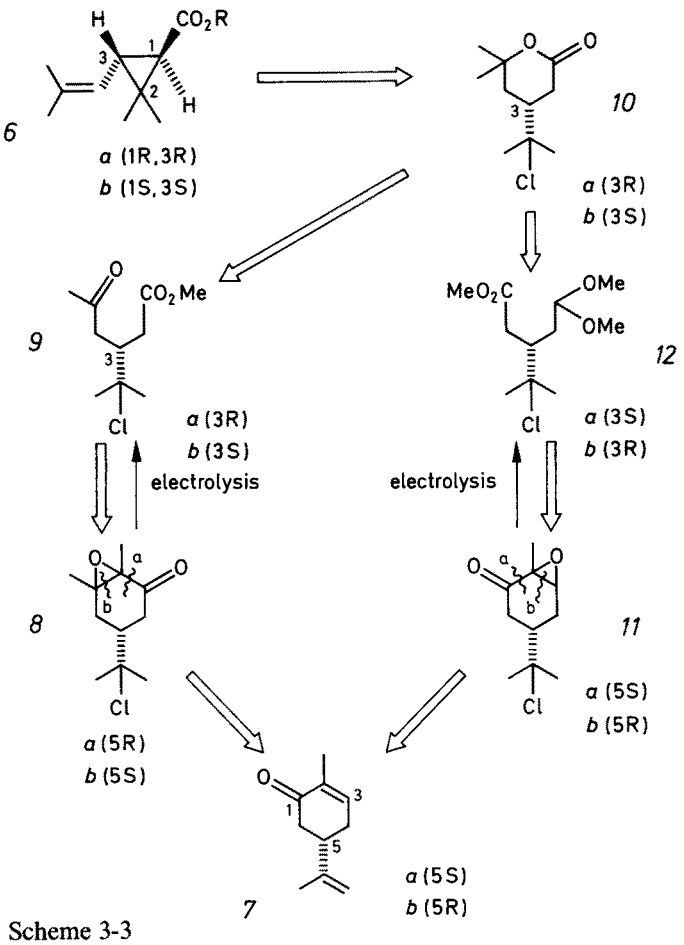
Scheme 3-2

The electrooxidative cleavage of *alpha,beta*-epoxycycloalkanone systems has been applied to the synthesis of optically active methyl *trans*- and *cis*-chrysanthemates *6* from (+)- and (—)-carvones *7* (Scheme 3-3) [51]. The double cleavage of 5-(1-chloro-1-methylethyl)-2,3-epoxy-2,3-dimethylcyclohexan-1-one *8* at the C-1/C-2 and C-2/C-3 bonds occurs in an MeOH— or MeOH/AcOEt (7:1)—$LiClO_4$—(Pt) system at an anode potential of 2.10–2.23 V vs. Ag/Ag^+ at 2–5 °C. The current efficiency is improved significantly using a cosolvent to increase the solubility of *8* in the solution. The electrooxidative carbon-carbon bond cleavage of *11*, which lacks the C-3 methyl of *8*, does not proceed under the electrolysis conditions used for *8*. However, if *13* and

Table 3.1 Conditions and Results of Electrooxidation of *8* [51]

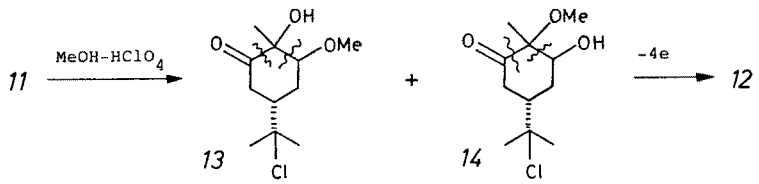
Entry	Substrate	Solvent[a]	Electrolyte	Product (Yield, %)
1	*8*	A	$LiClO_4$	*9* (87)
2	*8*	A	$LiBF_4$	*9* (85)
3	*8*	A	CF_3CO_2Li	*9* (16)
4	*8*	B	Et_4NOTs	*9* (0)[b]

[a] Solvents: A, MeOH—AcOEt (7:1); B: MeOH. [b] Epoxy ring-opened products were produced in 61% yield.



Scheme 3-3

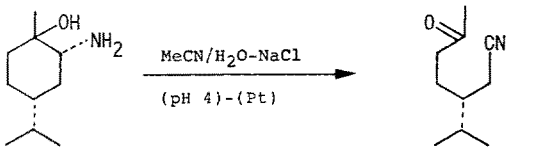
14, prepared by an acid-catalyzed hydrolysis of *11* in methanol, are electrolized in an MeOH—$LiClO_4$—(Pt) system, the desired *12* is formed in 87% yield (Scheme 3-4).



Scheme 3-4

Particularly noteworthy is the effect of the supporting electrolyte. The effect of strong electrolytes has been observed in the cleavage reaction of the *alpha,beta*-epoxycycloalkanones *8* and *11*. As shown in Table 3.1, entries 1 and 2, the use of $LiClO_4$ or $LiBF_4$ as a supporting electrolyte facilitates the formation of cleavage product *9* [51]. Lithium trifluoroacetate is less effective in producing *9* (entry 3). In contrast, the electrolysis of *8* with tetraethylammonium tosylate produces only the products of the epoxy ring opening together with the starting material *8* (28%) (entry 4).

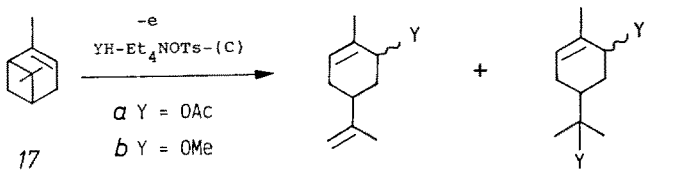
The electrolysis of 2-amino-1-cycloalkanol *15* in an MeCN/H_2O—NaCl—(Pt) system at pH 4 (buffered) yields keto nitrile *16* in 62% yield (Scheme 3-5) [52]. The formation of *16* can be explained by fragmentation of the intermediate *beta*-hydroxy-*N*-chloroamine and the subsequent further oxidation with $[Cl]^+$.



15 *16*

Scheme 3-5

The electrooxidation of *alpha*- and *beta*-pinenes in an AcOH—Et_4NOTs—(C) system affords ring-opened products [53]. For example, the electrolysis of *alpha*-pinene *17* gives carveols *18* and *p*-menth-6-ene-2,8-diol derivatives *19* (Scheme 3-6).

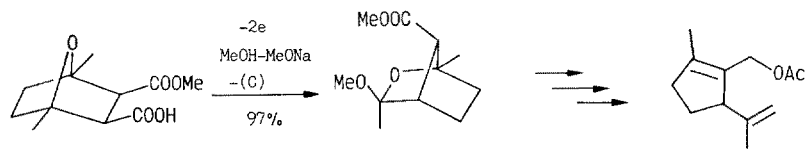


17 *18a* 24.4% *b* 21.8% *19a* 12.1% *b* 40.8%

Scheme 3-6

The formation of the ring-opened products by the electrooxidation may be explained by one-electron oxidation to the cation radical followed by C—C bond cleavage forming a tertiary carbenium ion and an allyl radical. Deprotonation, further one-electron oxidation, and attack of the nucleophile yield *18* and *19*.

Electro-decarboxylation of endo-3-methoxycarbonyl-7-oxabicyclo[2.2.1]heptane-endo-2-carboxylic acid *20* in an MeOH—MeONa—(C) system gives exclusively an oxygen-assisted Wagner-Meerwein rearrangement via the intermediate carbenium ion forming *21* in 83% yield [54]. Product *21* can be transformed to iridoid monoterpenes *22* (Scheme 3-7) [54a].

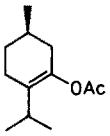
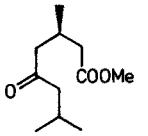
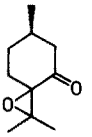
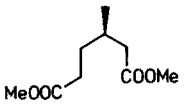
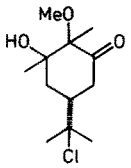
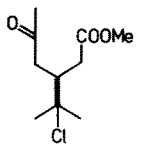
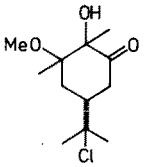
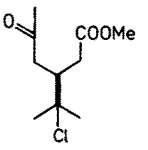
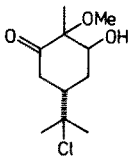
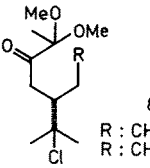
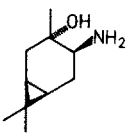
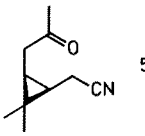
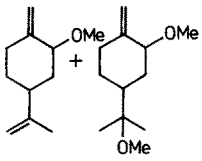
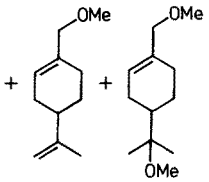


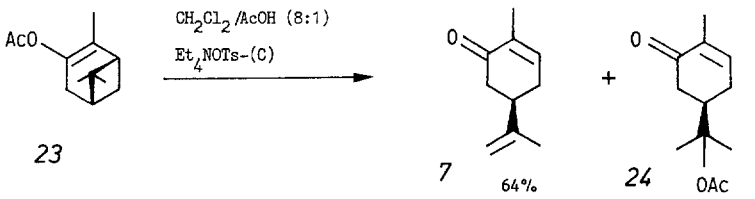
20 *21* *22*

Scheme 3-7

The electrooxidation of the enol acetate *23* of isopinocamphone generally leads to three different types of products: *l*-carvone *7*, 8-acetoxy-*p*-menth-6-en-2-one *24*, and 2-acetoxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-one. The product distribution is largely dependent on the combination of solvent and electrolyte. It is found that the enol acetate *23* leads to *l*-carvone *7* selectively, if electrolysis is performed in a CH_2Cl_2/AcOH(8/1)—Et_4NOTs—(C) system (Scheme 3-8) [55].

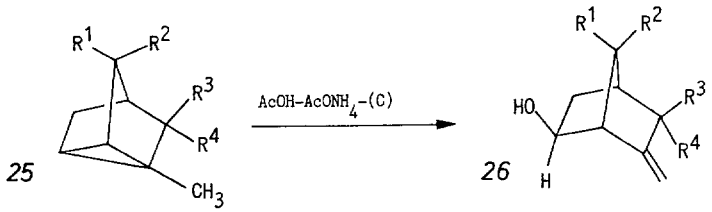
Table 3.2 Examples of the Electrooxidative Cleavage of Carbon-Carbon Bonds

Substrate	Electrolysis Conditions	Products Yield, %	Ref.
	MeOH/AcOH (10:1) – $LiClO_4$ – (Pt)	 74%	48)
	MeOH/AcOEt (7:1) – $LiClO_4$ – (Pt)	 83%	51)
	MeOH – $LiClO_4$ – (Pt)	 94%	51)
	MeOH – $LiClO_4$ – (Pt)	 96%	51)
	MeOH – $LiClO_4$ – (Pt)	 80% R : CHO R : $CH(OMe)_2$	51)
	MeCN/H_2O – NaCl – (Pt) buffer (pH 4)	 50%	52)
	MeOH – Et_4NOTs – (C)	 2.5% 7.4%	53)
		 14.7% 23.4%	



Scheme 3-8

Electrooxidative ring opening of polycyclic terpenoids *25* has been investigated in an AcOH—Et_3N—(C) system in an undivided cell. The electrolysis of tricyclene *25a* at 15 °C yields exo-2,2-dimethyl-3-methylenebicyclo[2.2.1]heptan-5-ol *26a*, Nojigiku alcohol, in 76% yield (Scheme 3-9) [56]. The results reported on the electrooxidative cleavage of terpenoids are summarized in Table 3.2.



a R^1=R^2=H, R^3=R^4=CH_3 (tricyclene) — *a* 76%

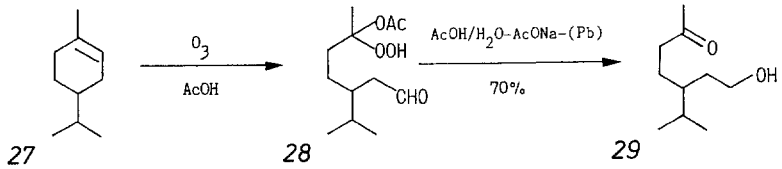
b R^1=R^2=CH_3, R^3=R^4=H (cyclofenchene) — *b* 77%

c R^1=H, R^4=CH_3, R^2—R^3=-$C(CH_3)_2(CH_2)_3$- (longicyclene) — *c* 85%

Scheme 3-9

3.1.2 Double Bond Cleavage under an Ozonization-Electroreduction Sequence

Electrochemical reduction of the ozonization products from monoterpenes, i.e., *p*-meth-1-ene, (+)-limonene, (+)-*alpha*-pinene, (+)-car-3-ene, provides the corresponding double-bond cleavage products in 45–70% yields [57]. The electrolysis of the acetyloxy hydroperoxide *28* derived from *p*-menth-1-ene *27* is carried out in an AcOH/H_2O(6/1 v/v)—AcONa—(Pb/Pb) system at −1.1 to −1.4 V vs. SCE, 2.0 to 2.2 A/dm^2 in a divided cell to give the corresponding keto-alcohol *29* in 70% yield (Scheme 3-10).



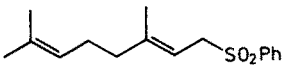
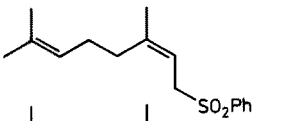
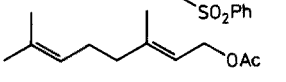
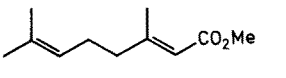
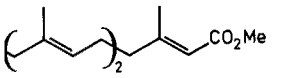
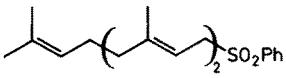
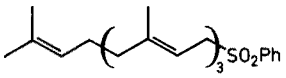
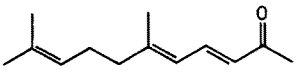
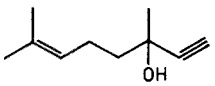
Scheme 3-10

3.2 Epoxydation of Double Bonds

3.2.1 Bromide-Assisted Anodic Epoxydation of Open-Chain Terpenoids

omega-Epoxypolyisoprene derivatives are a prominent class of synthetic intermediates for alicyclic terpenoids because of their ability for biogenetic-type cyclizations.

Table 3.3 Yields of ω-Epoxypolyisoprenoids and Reaction Conditions [58]

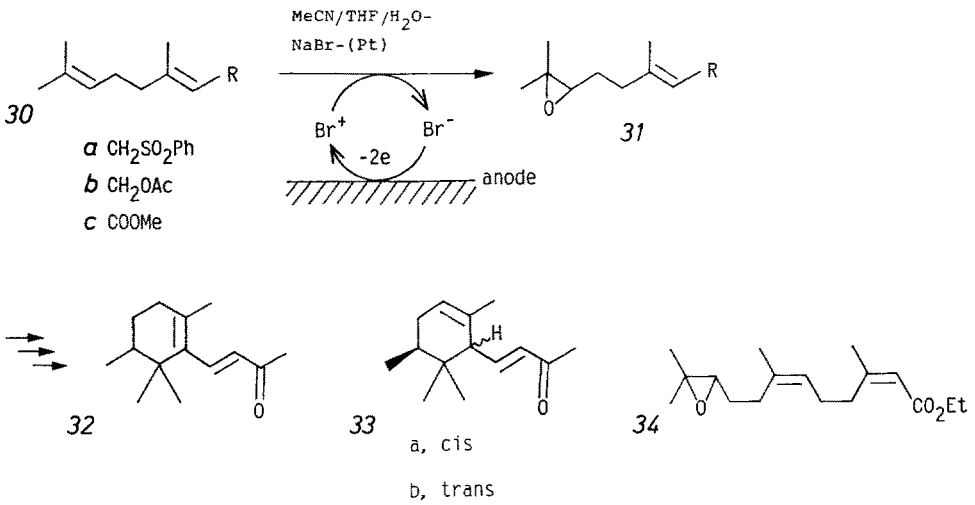
Substrate[a]	NaBr mmol	Solvent ml	Current mA	coulomb F/mol	ω-Epoxide Sel.[d]	(Conv) %
	0.2	MeCN—H_2O 7.5/1.5	10	3.6	99	(89)
	0.3	MeCN—THF—H_2O 5/2.5/1.5	10	3.0	85	(100)
	0.12	MeCN—THF—H_2O[b] 5/2.5/2	20	4.7	91	(82)
	0.05	MeCN—THF—H_2O 5/2.5/2	10	3.0	92	(80)
	0.05	MeCN—THF—H_2O 5/2.5/2	10	2.0	94	(46)
	0.6	MeCN—THF—H_2O 5/2.5/2	5	4.0	79	(64)
	0.6	MeCN—H_2O 7.5/1.5	5	4.0	81	(53)
	0.1	MeCN—THF—H_2O 5/2.5/2	10	2.0	88	(46)
	0.33	MeCN—H_2O[c] 0.5/8	10	3.5	77	(100)

[a] Substrate (0.1 mmol) is used for each electrolysis. [b] Triethylamine (0.5 eq) is added. [c] Formic acid (1 eq) is added. [d] Selectivity.

A regioselective *omega*-epoxidation of isoprenoids has been realized by the sodium bromide-assisted electrooxidation in an MeCN/THF/H_2O system in an undivided cell [58]. Electrolysis conditions and results are listed in Table 3.3. In general, the epoxidation of olefins proceeds smoothly in neutral or basic media while bromohydrination occurs preferentially in acidic media [59]. The effect of bromide salts is in the following order: NaBr (91%) > Et_4NBr (82%) > KBr (78%) > LiBr (75%) ≫ NH_4Br (13%); the yields of *31b* (R = CH_2OAc) are based on the consumed starting material.

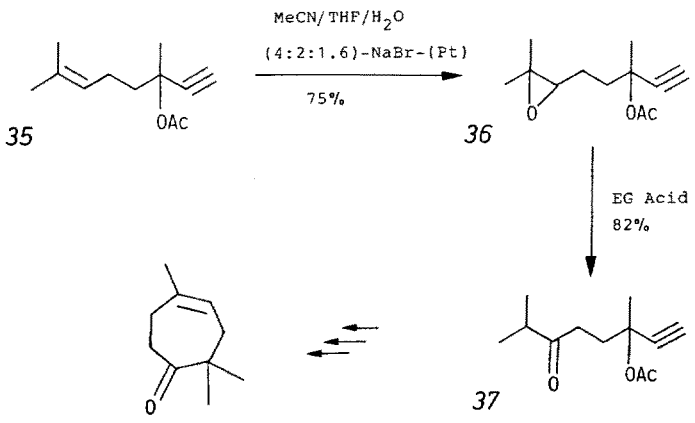
The electrochemical epoxidation of *30a* (R = CH_2SO_2Ph) proceeds smoothly to give 6,7-epoxy-3,7-dimethyl-1-(phenylsulfonyl)-2-octene *31a* (R = CH_2SO_2Ph) in

88% yield (Scheme 3-11) [60]. The electrochemical conversion of *30a* to *31a* is superior to the NBS (69%) and *m*-CPBA oxidation (72%) methods. The epoxide *31a* may be transformed to the *beta-*, *alpha-cis-*, and *alpha-trans*-irone (*32*, *33a*, and *33b*) known as important odorous components of orris root oils [60]. In a similar fashion, *omega*-epoxidation of ethyl Z,Z-farnesoate gives the corresponding epoxide *34* in 70% yield [61].



Scheme 3-11

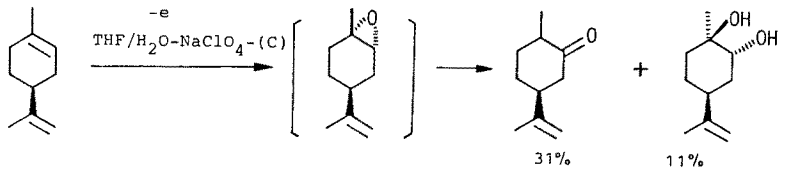
The epoxidation of dehydrolinalyl acetate *35* provides the corresponding epoxide *36* (75%) which can lead to karahanaenone *38*, a key odorous component of hop oil [62]. The epoxide *36* can be converted to the keto acetate *37* (82%) by an electrogenerated acid (EG Acid)-catalyzed rearrangement. Hydrogenation followed by alkaline hydrolysis of *37* gives 6-hydroxy-2,6-dimethyl-7-octen-3-one (86%) and subsequent thermal dehydration at 200 °C affords *38* (Scheme 3-12).



Scheme 3-12

3.2.2 Functionalization of Alicyclic Terpenoids

The electrooxidation of (+)- or (—)-limonene *39* in a $THF/H_2O(25/1)$—$NaClO_4$—(graphite) system gives a 2:1 mixture of the corresponding dihydrocarvone *41* and 1-hydroxyneodihydrocarveol *42 via* a protonated intermediate of *40* (Scheme 3-13)[63a].



39 *40* *41* *42*

Scheme 3-13

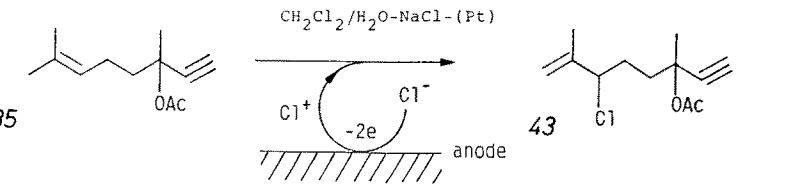
Independently, the epoxide *40* has been synthesized by electrolysis of *39* in a THF/H_2O—NaOH—(C) system, yielding a 5:1 mixture of *cis*- and *trans*-isomers. The stereoselective formation of *40* is explained by assuming the existence of a heterogeneous process caused by the absorption of limonene, which takes place on one of the sides of the double bond on a graphite electrode. The platinum anode does not work efficiently for the same conversion.

Electrooxidation of (—)-*alpha*-phellandrene in a $THF/H_2O(15/1)$—$H_2SO_4/NaClO_4$-(graphite) system can lead to (+)-*trans*-yabunikkeol, 1(7),2-*p*-menthadiene-6-ol, in 40% yield [63b].

3.3 Electrochemical Chlorination

3.3.1 Ene-Type Chlorination of Terpenoids

A regio- and chemoselective ene-type chlorination of isoprenoids has been realized by electrolysis in a CH_2Cl_2/H_2O—NaCl—(Pt) two-phase system. The electrochemical chlorination of dehydrolinalyl acetate *35* forms the ene-type chlorinated product *43* in 91% yield (Scheme 3-14) [64]. The product selectivity of the ene-type chlorination is

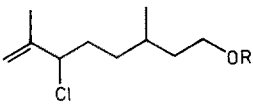
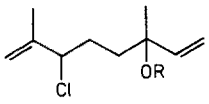
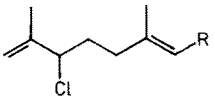
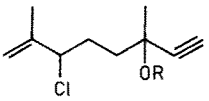
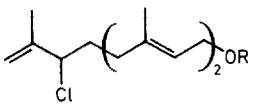
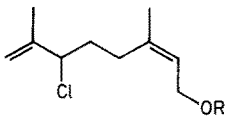
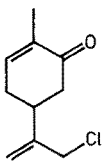


35 *43*

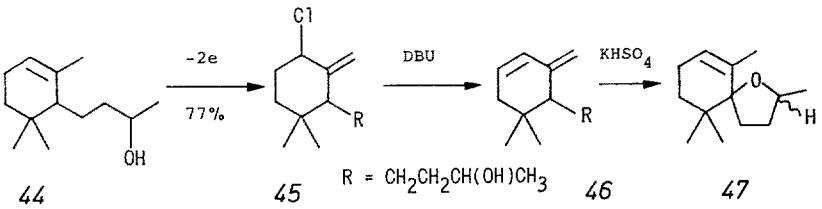
Scheme 3-14

highly dependent on the choice of halide ions and solvent systems. For example, the use of sodium chloride in a CH_2Cl_2—H_2O system gives the chloride *43*, exclusively, but sodium bromide leads to a mixture of epoxide, bromohydrine, and dibromide. Acetyl, ethynyl, methoxycarbonyl, and sulfonyl groups are inert in the course of the electrolysis. Some of the chlorinated products are shown in Table 3.4. The ene-type chlorination and subsequent dehydrochlorination is very useful for diene preparation. For example, electrolysis of *44* provides *45* (77%) which undergoes dehydrochlorina-

Table 3.4 Results of Electrochemical Ene-Type Chlorination of Polyisoprenoids [64]

Product	Yield, %	Product	Yield, %
	86 (R = Ac) 78 (R = H)		92 (R = Ac) 61 (R = H)
	81 (R = CH_2OAc) 78 (R = CH_2OH)		91 (R = Ac) 61 (R = H)
	81 (R = CH_2SO_2Ph) 91 (R = CO_2Me)		75 (R = Ac) 54 (R = H)
	81 (R = Ac) 61 (R = H)		75

tion by the action of DBU in DMF to form *46*. Subsequent cyclization of *46* gives *dl*-theaspirane *47* as an epimeric mixture at the C-2 position (Scheme 3-15).

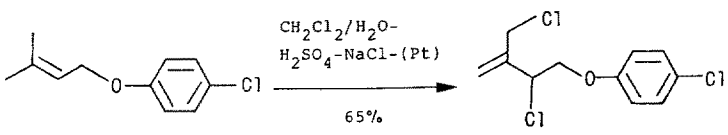


44 *45* R = $CH_2CH_2CH(OH)CH_3$ *46* *47*

Scheme 3-15

3.3.2 Electrochemical Double Ene-Type Chlorination

The isopropenyl chloride formed by ene-type chlorination usually is not reactive under the electrolysis conditions because of the strong electron-withdrawing nature of chlorine atom. However, 1-(4-chlorophenoxy)-3-methyl-2-butene *48* undergoes double ene-type chlorination to give *49* by electrolysis (10 F/mol) in the presence of acids in 65–70% yields (Scheme 3-16) [65].



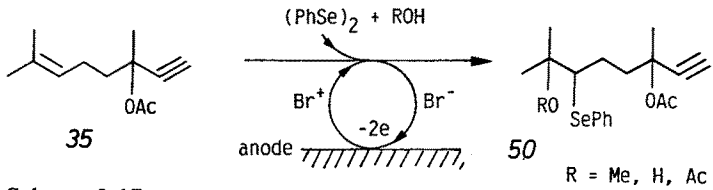
48 *49*

Scheme 3-16

3.4 Functionalization with Selenating Reagents

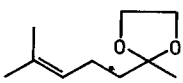
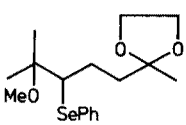
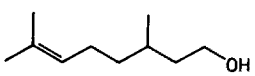
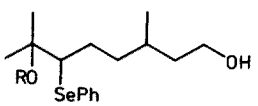
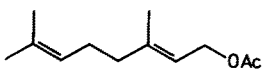
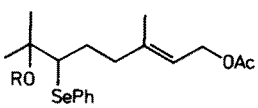
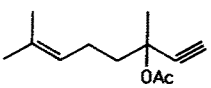
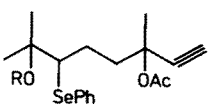
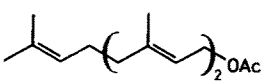
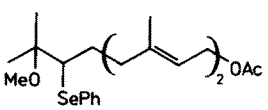
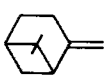
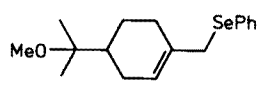
3.4.1 Oxyselenation of Terpenoids

Oxyselenides of terpenes have been electrochemically synthesized in high yields and with high regioselectivity in an MeOH (or AcOH, H_2O/MeCN)—R_4NX (X = Cl, Br, I)—$(PhSe)_2$—(Pt) system in the presence of a small amount of sulfuric acid (Scheme 3-17). The oxyselenation proceeds through regenerating a halonium ion



Scheme 3-17

Table 3.5 Electrochemical Oxyselenation of Isoprenoids [66]

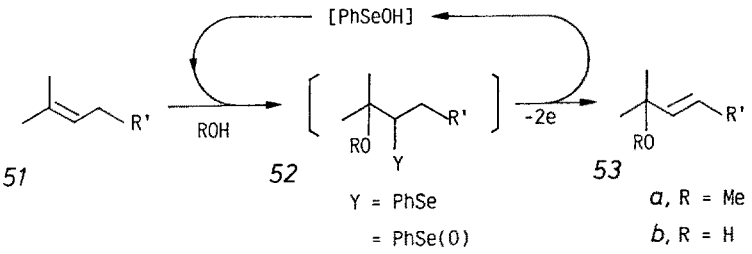
Olefin	Electricity F/mol	Selenide	Yield[a] %	Isomer[b] ratio
	4.2[c]		80	100/0
	2.5 3.0		Me 90 H 91[d]	99.5/0.5 98/2
	2.3 2.6		Me 83 H 80[d]	100/0 98/2
	2.0 3.0		Me 91 H 93[d]	99/1 99/1
	1.7		56	98/2
	2.0		63	100/0

[a] Yield based on isolated products
[b] (Markownikoff)/(anti-Markownikoff adduct)
[c] Pyridine (0.14 mol eq) is used
[d] MeCN—H_2O = 6 ml – 2 ml

in situ in the electrolysis system. For instance, a mixture of olefinic terpenoids *35*, diphenyl diselenide, tetraethylammonium bromide, and sulfuric acid in methanol is electrolyzed at room temperature under a constant current (70 mA/cm^2, 2.0 F/mol) in an undivided cell [66]. Most olefins can be functionalized to the corresponding methoxy, hydroxy, and acetoxyselenides *50* in high yield and regioselectivity (Markownikoff-type adduct). Some results are summarized in Table 3.5. Besides bromide ions, both chloride and iodide ions can be used for the reaction although in the latter case the current efficiency is somewhat poor. The voltammetric study reveals that initially the bromide ion is oxidized and neither $(PhSe)_2$ nor olefins.

3.4.2 Oxyselenation-Deselenation Sequence Leading to 3-Oxy-1-enes

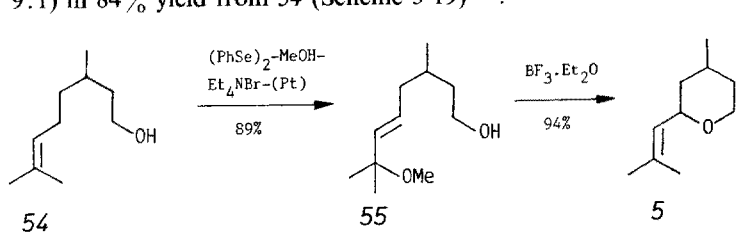
One-step transformation of olefins *51* into allylic alcohols *53b* (R = H) or ethers *53a* (R = Me) has been accomplished by an electrooxidative oxyselenation-deselenation sequence [67]. Furthermore, regeneration of the selenating reagent *in situ* has been accomplished by electrolysis in an $MeCN/H_2O(3/1)—Et_4NBr—(PhSe)_2—(Pt)$ system in the presence of magnesium sulfate under constant current (10 mA/cm^2, 8 F/mol) in an undivided cell [68]. Most of the terminal double bonds of isoprenoids *51* undergo the oxyselenation-deselenation reaction to give either *trans*-allylic alcohols *53b* (R = H) in aqueous acetonitrile or methyl ethers *53a* (R = Me) in methanol. The electrooxidatively generated phenylselenyl reagents (PhSeOR, R = H or Me) react regioselectively with olefins producing oxyselenide *52* (Y = PhSe) first, and the subsequent electrooxidation provides the corresponding selenoxide *52* (Y = PhSe(O)), which instantaneously undergoes *syn*-elimination to give *53* (Scheme 3-18). Phenyl-



Scheme 3-18

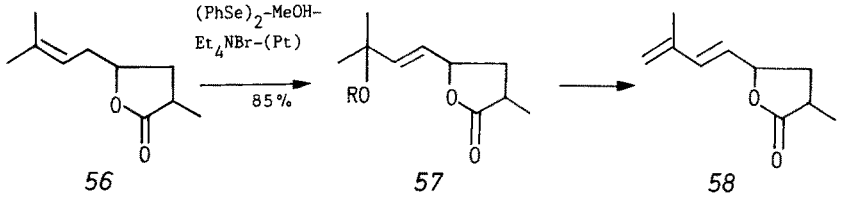
selenic acid generated by *syn*-elimination of the corresponding selenoxide is recycled during the electrolysis.

The electrolysis of citronellol *54* in methanol provides *55* (89% yield) and subsequent demethoxylative cyclization with BF_3-etherate (or EG Acid) gives *dl*-rose oxide *5* (*cis*/*trans* = 9:1) in 84% yield from *54* (Scheme 3-19) [67].



Scheme 3-19

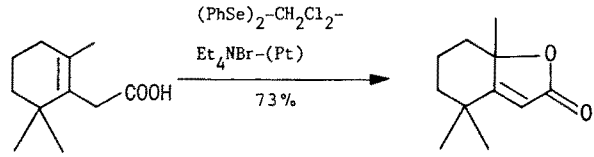
The functionalization of the lactone *56* in an $MeCN/H_2O(3/1)—Et_4NBr—(PhSe)_2—(Pt)$ system gives *57* (R = H) in 85% yield and the following methanesulfonylation of the alcohol forms *dl*-marmelolactone *58* (Scheme 3-20) [67].



56 *57* *58*

Scheme 3-20

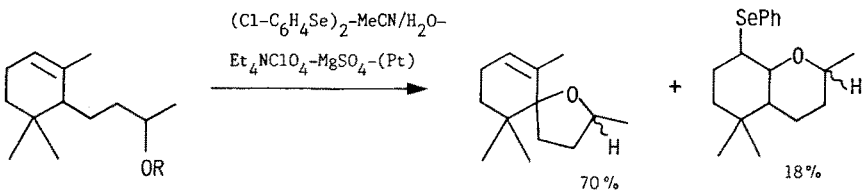
The synthetic applicability of the electrochemical oxy-transposition may be demonstrated by the one-step synthesis of *dl*-dihydroactinidiolide *60* from the carboxylic acid *59* in 73% yield. The lactone *60* may be produced by electrochemical intramolecular oxyselenylation followed by elimination of selenic acid (Scheme 3-21) [68].



59 *60*

Scheme 3-21

The electrochemical behavior of *dl*-dihydroionol *44* is interesting. The ester *44* (R = Ac) is unusually inert to the oxidation, however, the alcohol *44* (R = H) smoothly undergoes electrolytic spiroannelation and pyran-ring formation leading to *47* (70%) and *61* (18%) in an $MeCN/H_2O—Et_4NClO_4/MgSO_4—(Pt)$ system (Scheme 3-22) [69,70].



44 *47* *61*

Scheme 3-22

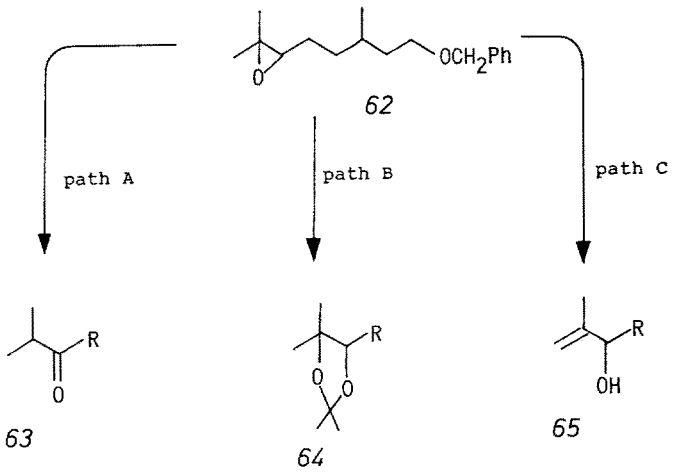
A straightforward method for the preparation of (2*R*)-4-(benzyloxy)-2-methyl-1-butanol from (*S*)-citronellol *54* by an electrochemical oxyselenation-deselenation sequence as a key step has been developed [71].

3.5 Electrogenerated (EG) Acid-Catalyzed Functionalization

3.5.1 EG Acid-Catalyzed Conversion of Epoxides

Potential features of EG acid chemistry have been well documented in the literature [72]. EG acid-catalyzed epoxide ring opening provides a versatile tool for synthetic functionalization of complex molecules. Three different rea' 'ion pathways may be follow-

ed. For instance, 6,7-epoxy-3,7-dimethyloctyl benzyl ether *62* can be directed to three different products *63*, *64*, and *65* under appropriate electrolysis conditions (Scheme 3-23).



Scheme 3-23

The conversion of *62* into *63* can be realized in 91% yield by electrolysis in a CH_2Cl_2/THF—$LiClO_4$—(Pt) system in an undivided cell along with 8-benzyloxy-2,6-dimethyloct-1-en-3-ol *65* (8%) as a side-product [73].

The EG acid-catalyzed conversion of *62* into the acetonide *64* proceeds upon electrolysis in an acetone-$Mg(ClO_4)_2$—(Pt) system at room temperature. The selectivity of the acetonidation can be strictly controlled by the concentration of electrolytes [73]. The results are shown in Table 3.6.

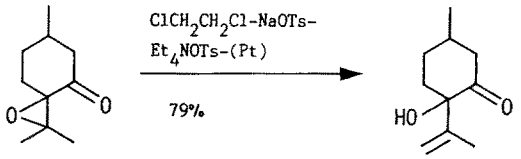
Table 3.6 Conditions and Results of EG-Acid Catalyzed Reaction [73]

Path	Conditions	Product, Yield %		
		63	*64*	*65*
A	CH_2Cl_2/THF (7.5/0.5)-$LiClO_4$—(Pt)	91		8
B	Acetone-$Mg(ClO_4)_2$—(Pt)		86	
C	$ClCH_2CH_2Cl$—NaOTs—Et_4NOTs—(Pt)	2		86

An epoxide-allyl alcohol rearrangement occurs in a $ClCH_2CH_2Cl$—Et_4NOTs—NaOTs—(Pt) system. The electrolysis of *62* is carried out at 2.7 mA/cm^2 (0.4 F/mol) at room temperature with additional stirring for 90 min to give the allyl alcohol *65* in 86% yield together with the ketone *63* (2%) [74]. The intermediate carbenium ion is probably trapped initially by electrogenerated unbuffered tosylate ions, giving rise to a tertiary tosylate, which is so labile that spontaneous E_1-type elimination affords the allyl alcohol *65*.

EG acid-assisted isomerization of the epoxide *66* can lead to the formation of the

corresponding allyl alcohol *3* by electrolysis in a $ClCH_2CH_2Cl$—Et_4NOTs—NaOTs—(Pt) system (Scheme 3-24).



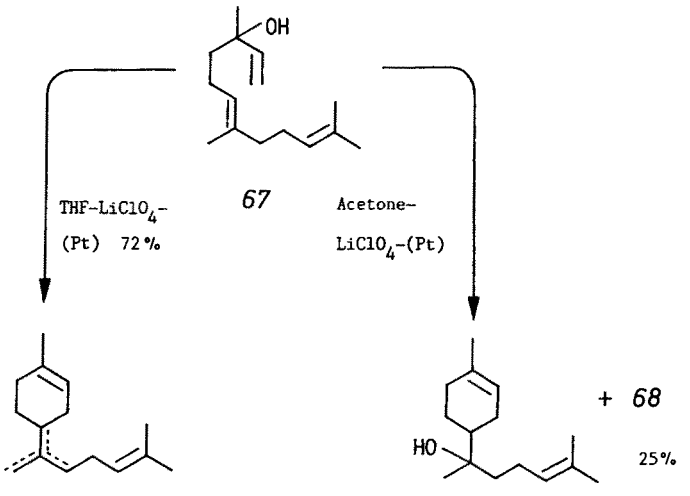
66 *3*

Scheme 3-24

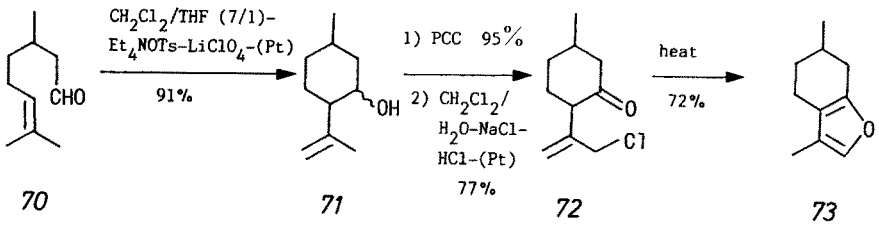
3.5.2 EG Acid-Catalyzed Cyclization

The transformation of *dl*-nerolidol *67* into *dl*-bisabolol *69* is a successful example of EG acid-catalyzed cyclization of acyclic compounds [75].

The best result so far available through a non-EG-acid approach has been obtained with 100% formic acid leading to the desired *69* in 32% yield after alkaline hydrolysis. In contrast, the electrolysis of *67* in an acetone—$LiClO_4$—(Pt) system at constant current (3.3 mA/cm^2 for 1 h, 0.36 F/mol) in an undivided cell affords the desired alcohol *69* in 52% yield together with *68* (25%) (Scheme 3-25). The effect of the solvent is remarkable. Acetone is suitable for the selective preparation of *69*, presumably because it traps the cationic intermediate, leading to an oxocarbenium ion, which



Scheme 3-25



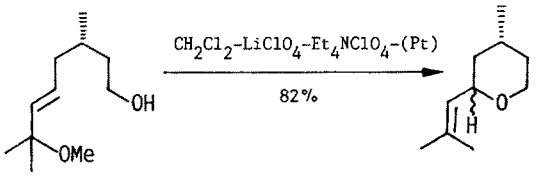
70 *71* *72* *73*

Scheme 3-26

is probably stabilized by an unbuffered perchlorate ion. The electrolysis in THF at 60 °C and/or in $ClCH_2CH_2Cl$/THF(9:1) at 50 °C provides *68* in 66–72% yields.

EG acid-catalyzed cyclization of citronellal *70* in a CH_2Cl_2/THF(7/1)—Et_4NOTs/$LiClO_4$—(Pt) system gives a 91% yield of the cyclized products *71*, a precursor for the synthesis of menthofuran *73 via* the ene-type chlorination product *72* (Scheme 3-26) [72a].

The EG acid-catalyzed demethoxylative cyclization of the olefin alcohol *55* prepared by electrochemical oxyselenation-deselenation of *l*-citronellol proceeds in a CH_2Cl_2—$LiClO_4$/Et_4NClO_4 system to give *l*-rose oxide *5* in 82% yield (Scheme 3-27) [72a].



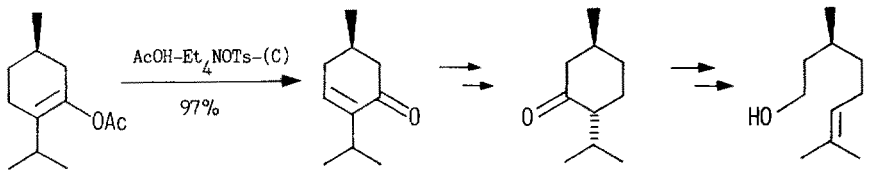
55 *5*

Scheme 3-27

3.6 Functionalization of the Double Bond of Terpenoids

3.6.1 Oxidative Conversion

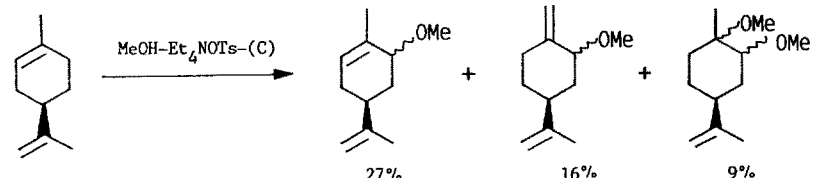
Alicyclic enol acetates can lead to the corresponding enones by anodic oxidation. The electrolysis of *d*-menthenyl acetate *74* in an AcOH—Et_4NOTs—(C) system by passing 2.5 F/mol of electricity provides the *d*-menthenone *75*, a precursor for *d*-menthone *76* and *l*-citronellol *54* syntheses, in 97% yield (Scheme 3-28) [76a].



74 *75* *76* d-menthone *54* l-citronellol

Scheme 3-28

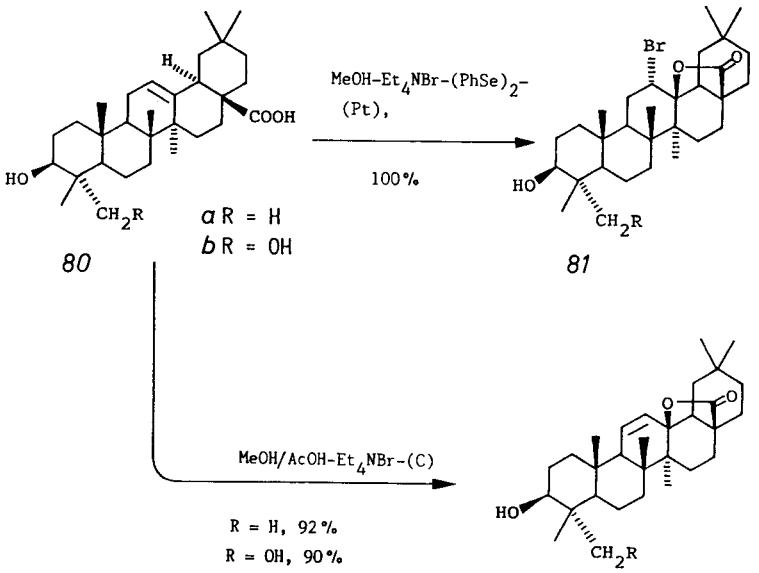
The electrooxidation of limonene *39* in an MeOH—Et_4NOTs—(C) at 1.4–1.5 V vs. SCE forms a mixture of products *77–79* which are formed by oxidation of the *intra*-ring double bond of *39* only (Scheme 3-29) [76b].



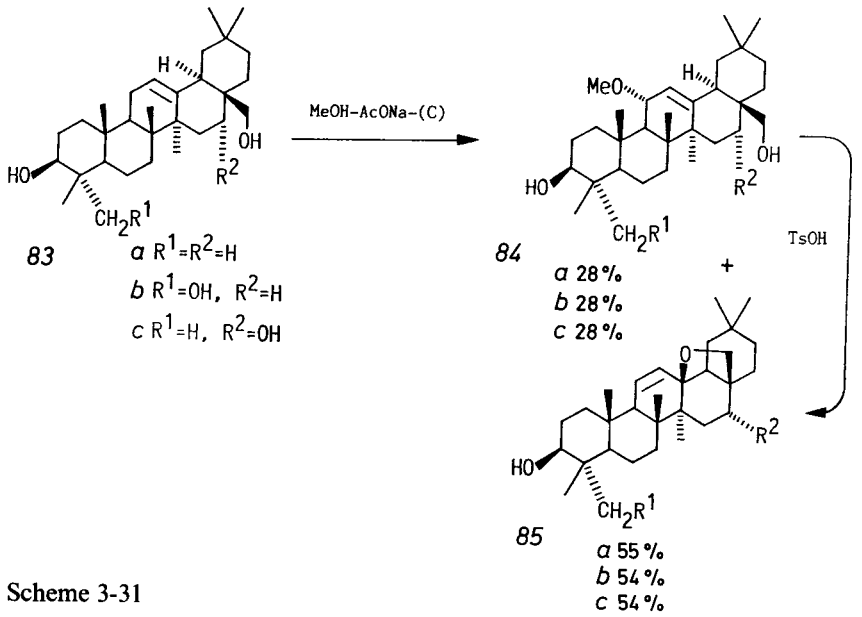
39 *77* 27% *78* 16% *79* 9%

Scheme 3-29

Electrooxidation of *alpha*-dihydroionol in an MeOH—$LiClO_4$—(C) system at 1.25 V (SCE) can lead to the corresponding methoxylated products in 57% yield, whereas the electrolysis in an MeCN-1,6-Lutidine—(Pt) system at 1.6 V (Ag/Ag^+) resulted in edulan derivatives in ca. 23% yields. The electrolysis of *beta*-dihydroionol in either an MeOH—$LiClO_4$—(C) or an MeCN—H_2O—(Pt) system gives spiro compounds including 6-methoxy- and 6-hydroxydihydrotheaspiranes and theaspirane in 21–23% yields [77].



Scheme 3-30



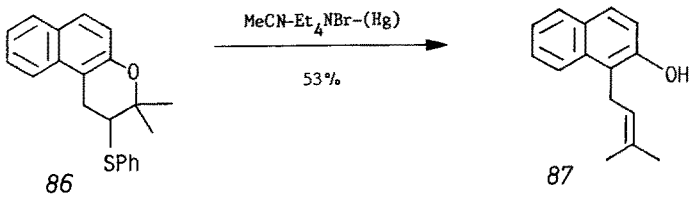
Scheme 3-31

Electrochemical bromo-lactonization of the triterpenoid oleanolic acid *80* has been performed in an MeOH—Et_4NBr/$(PhSe)_2$—(Pt) system to give 12*alpha*-bromo-28,13-*beta*-oleanolide *81* in quantitative yield. On the other hand, constant current electrolysis of *80a* or hederagenin *80b* in an MeOH/AcOEt—Et_4NBr—(C) system forms *82* in 90–92% yields (Scheme 3-30) [78a].

Allylic methoxylation is the first step in the anodic oxidation of olean-12-ene alcohols *83* [78a]. The electrolysis of erythrodiol *83a* in an MeOH—AcONa—(C) system forms a mixture of *84a* (28%) and *85a* (55%). The alcohols *84* can be exclusively converted into *85* on treatment with a *p*-TsOH-aq. dioxane system at 25 °C for 30 min (Scheme 3-31).

3.6.2 Reductive Functionalization

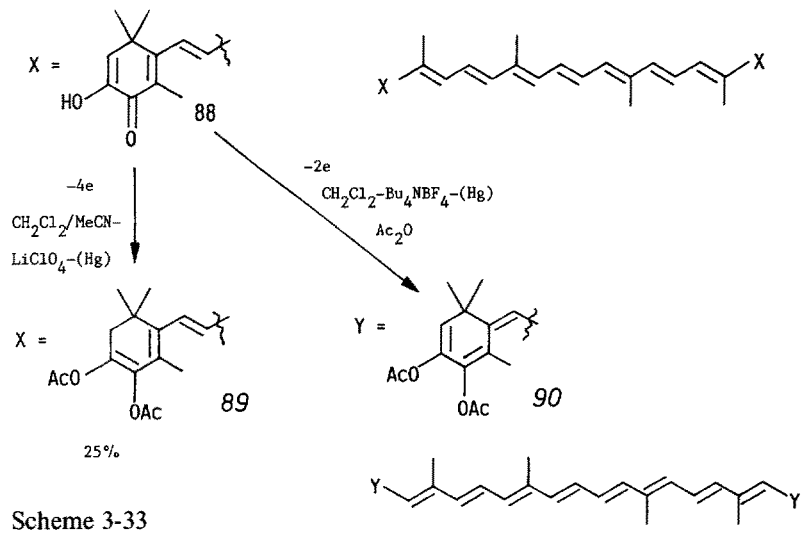
The *ortho*-prenylphenol substructure is the initial product of the biogenetic prenyl-pyrophosphate-phenol coupling. Many modifications of this structure are observed in nature. The electroreductive ring opening of 3-phenylthiochroman *86* in an MeCN—Et_4NBr—(Hg) system provides 1-isopent-2-enyl-2-naphthol *87* in 53% yield (Scheme 3-32) [79].



86 *87*

Scheme 3-32

Electroreduction of conjugated enone systems is a possible route for carotenoid synthesis. The electroreduction of astacene *88* gives *90* after passage of 2 F/mol of electricity in a CH_2Cl_2—Bu_4NBF_4—(Hg) system in the presence of acetic anhydride. Similar electrolysis of *88* in a CH_2Cl_2/MeCN—$LiClO_4$ system (4 F/mol of electricity) provides *89* in 25% yield (Scheme 3-33) [80].

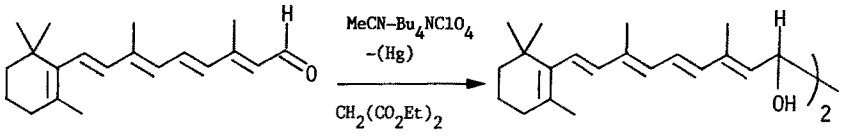


Scheme 3-33

3.7 Conversion and Formation of Carbonyl Functions

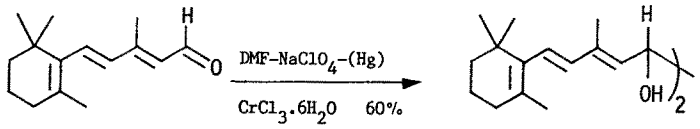
3.7.1 Electroreductive Hydrodimerization (Pinacolization)

Many attempts for the cathodic pinacolization of carbonyl compounds have been made for the synthesis of carotenoids. In general, the cathodic coupling of *alpha*, *beta*-unsaturated carbonyl compounds occurs predominantly at the *beta* position to give the corresponding 1,6-dicarbonyl compounds unless the *beta* position is hindered. However, ionones *93* and *95* and retinal *91* undergo smooth pinacolization by virtue of steric hindrance at the *beta* position. Electroreduction of retinal *91* in an MeCN—Bu_4NClO_4—(Hg) system in the presence of excess diethyl malonate as a proton source gives the retinal pinacol *92* in 85% yield, while similar electrodimerization in solutions containing water, phenol, or acetic acid can lead to a mixture of less-conjugated



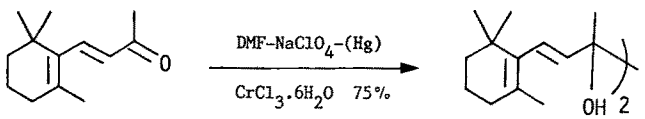
91 *92*

Scheme 3-34



93 *94*

Scheme 3-35



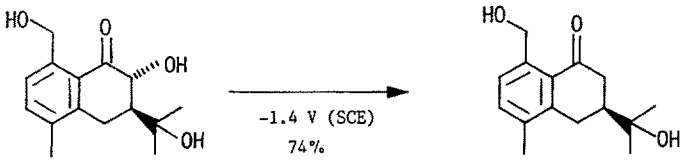
95 *96*

Scheme 3-36

dimeric products (Scheme 3-34)[81]. The pinacolization of *beta*-ionone *95* (Scheme 3-36), *beta*-ionylidene acetaldehyde *93* (Scheme 3-35), and retinal *91* in a DMF—$NaClO_4$—(Hg) system in the presence of chrominium (III) trichloride gives the corresponding pinacols *96*, *94*, and *92* in 75, 60, and 25% yields, respectively[82]. In these cases, Cr(III) enhances the pinacolization at the expense of formation of the corresponding alcohols. Furthermore, the relevant reduction potential is lowered. The proposed mechanism involves the formation of a complex between Cr(III) and the carbonyl compound combined with inner-sphere electron transfer between Cr(II) and Cr(III) species. Hydrodimerization of *alpha*- and *beta*-ionones *95* in aqueous media has recently been performed by using metallic tin as a promoter. Electrolysis of *alpha*-ionone in an MeOH/AcOH/H_2O—1*M*H_2SO_4—(Pt) system in the presence of tin (5–100 mol%) provides the corresponding dimer in 60–77% yields[83].

3.7.2 Reductive Deoxygenation

Controlled potential electrolysis of emmotin A *97* at −1.4 V vs. SCE furnishes the corresponding deoxygenated product, 2-deoxyemmotin A *98*, in 74% yield (Scheme 3-37) [84].

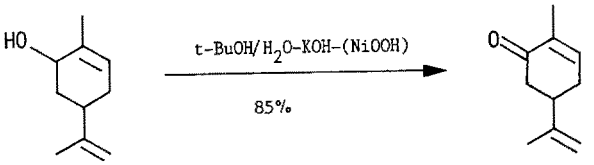


97 *98*

Scheme 3-37

3.7.3 Formation of Carbonyl Groups from Alcohols

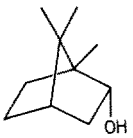
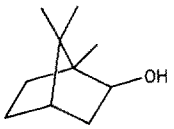
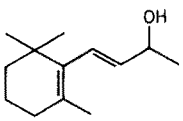
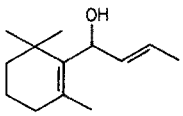
A versatile oxidation method for alcohols via electrochemically generated nickel oxide hydroxide is performed at a nickel hydroxide anode in alkaline media [85].



99 *7*

Scheme 3-38

Table 3.7 Oxidation of Secondary Alcohols to Ketones by NiOOH [85]

Alcohol	Time/Temperature/Current	Yield,%
	24h/25°/0.6 A	90
	34h/25°/0.4 A	90
	34h/25°/0.1 A	79
	68h/25°/0.2 A	9

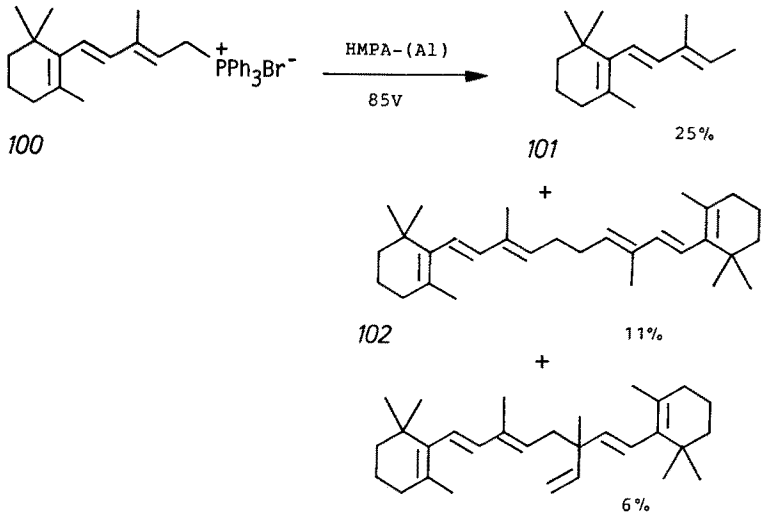
Electrolyte: 0.1 M KOH – 50% *t*-BuOH – 50% H_2O

The oxidation of secondary alcohols of terpenoids and steroids readily leads to the corresponding ketones. The electrolysis of carvenol *99* is carried out in a *t*-BuOH/H_2O(1/1)—KOH-(activated Ni) system at 2.4 mA/cm^2, 1.8–2.3 V in an undivided cell to give carvone *7* in 85% yield (Scheme 3-38) [85]. Some results are shown in Table 3.7.

3.8 Miscellaneous Conversions

3.8.1 Carbon-Carbon Bond Forming Reactions

The cathodic reduction of allylphosphonium salts gives mainly carbon-phosphor bond cleavage products. However, the electroreduction of a C_{15} polyenylphosphonium bromide *100* in a HMPA—(Al) system at 85 V provides the C—P bond cleavage product *101* (25%) along with coupling products *102* (11%) and *103* (6%) (Scheme 3-39) [86].

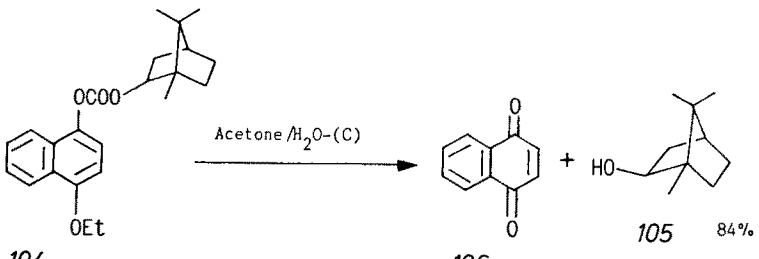


100 *101* *102* *103*

Scheme 3-39

3.8.2 Electrochemical Deprotection

The 4-ethoxy-1-naphthyloxycarbonyl group is a valuable electrochemically labile protecting group for alcohols and amines. The deprotection of borneol *105* and gerani-

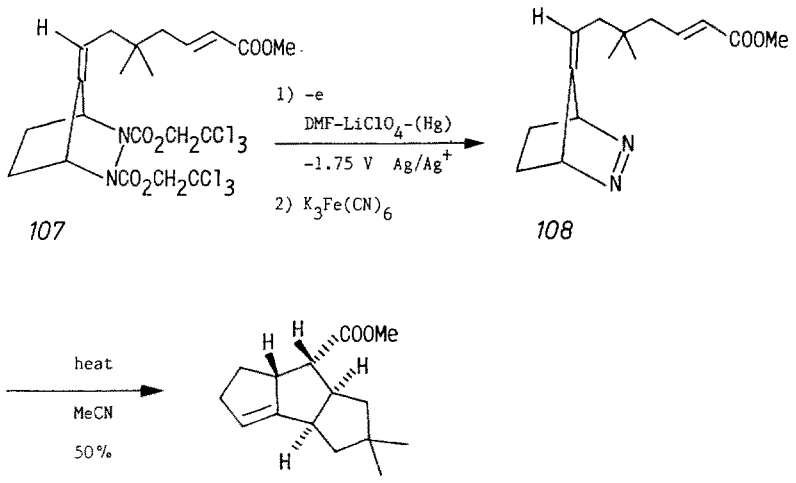


104 *106* *105*

Scheme 3-40

ol has been performed. The electrolysis of the naphthydroquinone derivative *104* of borneol *105* in an Acetone/H_2O—(C) system at ca. 1.6 V vs. SCE gives the deprotected borneol *105* in 84% yield (Scheme 3-40) [87]. Geraniol can be recovered by the deprotection in 67% yield.

The Diels-Alder adduct of fulvene and di(2,2,2-trichloroethyl)azodicarboxylate after selective monohydrogenation of the endocyclic *pi* bond can lead to the bicyclic biscarbamate *107*. The electrochemical removal of the *N*-protecting carbamoyl groups in a DMF—$LiClO_4$—(Hg) system is followed by the oxidation with potassium ferricyanide to give the azo compound *108* which on thermal decomposition forms the linearly fused tricyclopentanoid *109* in over 50% yield (from *107*, Scheme 3-41) [88a].

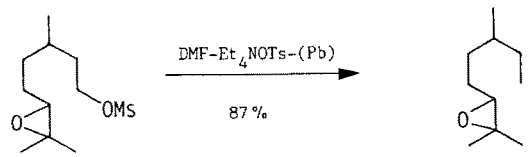


107 *108* *109*

Scheme 3-41

3.8.3 Removal of Methylsulfonyl and Carboxyl Groups

Electroreductive conversion of aliphatic alcohols to the corresponding alkanes has been developed. A variety of methanesulfonates of terpene alcohols can be successfully converted to the corresponding alkanes as shown in Table 3.8. The electrolysis of methanesulfonate *110* in a DMF—Et_4NOTs—(Pt/Pb) system in a divided cell at 5–10 °C provides the corresponding alkane *111* in 87% yield (Scheme 3-42) [89].

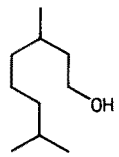
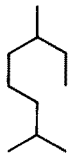
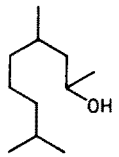
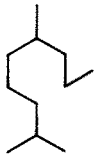
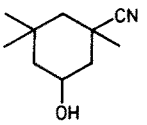
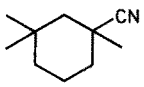
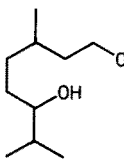
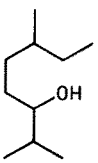


110 *111*

Scheme 3-42

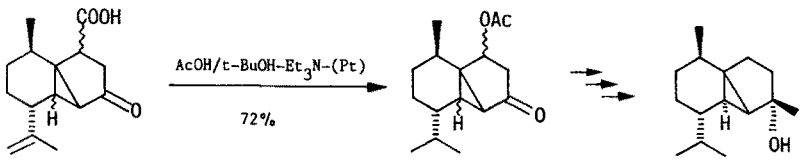
An electrochemical procedure for the replacement of carboxyl function by an acetoxy group at the C-2 carbon atom of a tricyclo[4.4.0.$0^{1,5}$]decan-4-one system has been realized [90]. The procedure is utilized as the key step for the synthesis of cubebol *114*

Table 3.8 Transformation of Alcohols to Alkanes through Methanesulfonates [89]

Alcohol	Electricity F/mol	Alkane	Yield, %
	4		85
	4		63
	4		71
	4.8		72

Electrolysis conditions: DMF–Et_4NOTs–(Pb)

from *l*-carvone. The electrolytic acetoxylation of the carboxylic acid *112* in an AcOH/*t*-BuOH—Et_3N—(Pt) system at 1.6–1.7 V vs. SCE in an undivided cell provides the corresponding acetoxylated product *113* in 72% yield as a sole product (Scheme 3-43) [91].



112 *113* *114*

Scheme 3-43

3.8.4 Other Reactions

Anodic mono- and dibromination of thymol has been shown to proceed selectively depending on the choice of solvent. Electrolysis in acetonitrile gives only 6-bromo-

thymol in 98% yield, whereas in methanol it provides selectively 2,6-dibromothymol in 90% yield [92].

The electrooxidation procedure has been used in the preparation of a key intermediate for the *dl*-helminthosporal synthesis [93]. Aromatic steroids have been functionalized by means of anodic substitution introducing nucleophiles in the benzylic position [94a] or at the aromatic nucleus [94b].

A stereoselective electroreductive cyclization has been used in the synthesis of *l*-sterpurene, an isolactarane-type sesquiterpene [95].

4 Concluding Remarks

To increase the inherent value of chiral biomolecules which are made available by natural resources or by fermentation procedures is one of today's highlights in the field of organic synthesis. During the last decade, as far as the organic synthesis is concerned, the electrochemical methodology has been exposed to strong competition by chemosynthetic methods as well as biosynthetic technologies. Such immanent pressure urges to contrive new, selective electrochemical techniques in order to demonstrate their superiority as compared with others in their practical application. Under these circumstances, the actual value of the electrochemical methodology as a tool for the conversion of biomolecules may be clarified in the near future.

5 Acknowledgement

We acknowledge the careful secretarial work of Youko Irie and Yuuko Fukushima, who arranged the data concisely and typed the manuscript cautiously.

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